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SURGERY OF LOWER ESOPHAGUS

Pathophysiological, experimental and
clinical aspects



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SURGERY OF LOWER ESOPHAGUS
Pathophysiological, experimental
and clinical aspects

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Leg läk, Lund

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Title and subtitle SURGERY OF LOWER ESOPHAGUS. Pathophysiological, experimental and clinical aspects.			
Abstract A new method to restore the alimentary tract after total gastrectomy, esophagojejunostomy end-to-side with a stapling device was developed in pigs. The stapled anastomosis was compared to a sutured concerning leakage frequency, breaking strength, anastomotic width, -circulation and collagen concentration. Except from being faster the stapled esophagojejunostomy was equal to the sutured regarding the above mentioned parameters. Based on these results the stapling device was used in a prospective series of 27 patients with the anastomoses in the abdomen or in the right or left chest and a mortality rate of 1/27 and leakage:3/27. The importance of different lower esophageal sphincter (LES) parameters for reflux to occur was studied in patients with paraesophageal and sliding hiatal hernias and in an unique in vitro model. It was shown that patients with a paraesophageal hernia and reflux had a short LES with normal tone but with virtually none of it exposed to abdominal pressure. In contrast patients with a sliding hiatal hernia and reflux had a poor sphincter tone and an inadequate intraabdominal sphincter segment. The in vitro model emphasized the importance of esophageal tension and gastric outlet diameter for cardiac competency. In 15 healthy volunteers it was illustrated how morphine significantly inhibited the relaxation of LES. In 43 patients with benign (23) or malignant (20) Barrett's esophagus successful antireflux surgery (benign cases) was followed by stabilization of dysplastic epithelial changes and squamous epithelial regeneration in some cases. The malignant potential was higher in men who smoked, in patients with intestinal-type metaplasia and who continued to smoke and have severe reflux and in patients with dysplasia.			
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From the Department of Surgery, Lund University,

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SURGERY OF LOWER ESOPHAGUS

Pathophysiological, experimental and clinical aspects

by

Bruno Walther

Lund 1985

To Birgitta, Louise, Charles
Inga and Stellan

The present thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

- I Healing of the esophagojejunal anastomosis after total gastrectomy in the pig.
B Walther, P Löwenhielm, S-E Strand, F Ståhlberg, B Uvelius and J Oscarson.
Submitted.
- II Esophagojejunostomy with the EEA-stapler.
B Walther, J Oscarson, H Graffner, S Vallgren and A Evander.
Submitted.
- III Effect of paraesophageal hernia on sphincter function and its implication on surgical therapy.
B Walther, T DeMeester, E Lafontaine, J Courtney, A Little and D Skinner.
Am J Surg 147:111-116, 1984.
- IV Gastric dilatation, intragastric pressure and esophageal tension as determinants of cardiac competency.
A Evander, B Walther, L Bonavina and T DeMeester.
Submitted.
- V Influence of morphine on the distal oesophagus and the lower oesophageal sphincter - a manometric study.
K Dowlatshahi, A Evander, B Walther and D Skinner.
GUT, in press 1985.
- VI Barrett's esophagus. Comparison of benign and malignant cases.
D Skinner, B Walther, R Riddell, H Schmidt, C Iascone and T DeMeester.
Ann Surg 198:554-566, 1983.

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INTRODUCTION

Esophagus, was long and still is by some surgeons considered a no mans land. In 1884 the first total gastrectomy was performed by the surgeon Conner (1). His patient died from shock in the operating room. Schlatter (2) in 1897 had the distinction of being the first surgeon to successfully resect the entire stomach. In 1929 Finney and Rienhoff (3) reviewed the cases published so far. They found 62 cases and added five of their own. Operative mortality rate was 54%. A higher recovery rate was noticed with esophagojejunostomy than esophagoduodenostomy.

After the development of techniques permitting safe intrathoracic operations the esophagogastric junction became more accessible for surgical procedures. Mikulicz (4) first report in 1898 of a one stage operation for a malignant lesion in the gastro-esophageal junction was followed by many unsuccessful attempts. It was not until 1933 that Ohsawa (5) reported his first survival after transpleural esophagogastrctomy with esophagogastrostomy end-to-side in a one stage procedure. It soon became obvious, in spite of many ingenious ways of anastomosing the esophagus to the rest of the gastrointestinal tract, that the incidence of anastomotic failures was high and the main reason for post-operative death (6). Therefore it is of great importance to study factors influencing the uneventful healing of the esophagojejunal anastomosis after total gastrectomy. The use of stapling devices for better anastomoses should be carefully and objectively assessed and, if proven safe and superior, recommended for clinical use.

In 1879 Quincke (7) first described the pathology of esophagitis, but it was not until 1935 it was thought to be of peptic origin (8). The connection between a herniated stomach and esophagitis was mentioned by Jackson, when discussing a paper by Winkelstein in 1935 (8). Despite large experimental and clinical research controversy still exists on the pathophysiology of the disease.

Surgical treatment of reflux esophagitis originates in 1951 when Allison (9) demonstrated an association between symptomatic sliding hiatal hernia and reflux. He reported a procedure aiming at correction of the hernia and thereby inhibiting reflux. The recurrence rate of esophagitis with this method was, however, high and the method was later abandoned (9). The best way for prevention of reflux of gastric contents has since been a source of great controversy. Many theories have been proposed to explain the pathophysiologic mechanisms and to justify different surgical methods. At present four operations are commonly used to correct gastroesophageal reflux. These are the Nissen (10) fundoplication, the Belsey (11) Mark IV procedure, Hills (12) trans-abdominal gastropexy and, finally, the insertion of an Angelchik (13) prosthesis around the lower esophagus. The first three

methods increase the intraabdominal length and resting pressure of the distal esophageal segment, factors thought to be important for maintaining cardiac competency (14, 15, 16). The use of the Angelchik prosthesis is based on a new concept, namely, insertion of a synthetic collar around the cardia. In spite of lack of conclusive evidence of its effectiveness it has been used with increasing frequency.

In some hiatal hernias, especially true paraesophageal, an adequate length of the lower esophageal sphincter (LES) is placed within the abdomen. These hernias are generally not associated with reflux (17, 18). This clinical observation has been challenged by others (19). Thus reflux can occur in patients with normal sphincter pressure and abdominal sphincter length. Obviously other mechanisms influencing cardia competency must be involved. Such factors include the neural and hormonal control of sphincter tonus. Studies elucidating these interrelationships are therefore of utmost importance before recommending a certain antireflux procedure.

In 1950 Barrett (20) described the condition of peptic ulceration in the esophagus arising in a zone of gastric type epithelium. Controversy has persisted since then concerning its etiology, classification and clinical management. In 1953 Morson and Belcher (21) reported the first case in which adenocarcinoma of the esophagus developed in an aberrant gastric-type mucosa. Since then the potential for the columnar-lined esophagus to undergo malignant degeneration has become well known. However, the mechanisms for progression from the benign to the malignant form have been poorly understood.

ANATOMY OF LOWER ESOPHAGUS

We define lower esophagus as the lower one third of the gullet including the cardia.

The esophagus is a tube connecting the pharynx and the stomach. Its upper end starts at the lower border of the sixth cervical vertebra. After passing through the diaphragm, the esophagus ends in the stomach at the level of the eleventh thoracic vertebra. During swallowing the points of fixation i.e. the upper and lower ends move cranial about two centimeters. The esophageal hiatus of the diaphragm is supported by muscular fibres forming the diaphragmatic crura. These arise as tendinous bands from the anterolateral surfaces of the first three or four lumbar vertebrae (Fig. 1). The celiac axis and the superior mesenteric artery separate the muscle bundles of the right and left crura. Often there is a prominent ligament (arcuate ligament) that unites the two crura anterior to the aorta just above the celiac artery (Fig. 1). In cadaver dissections (22) this ligament was found in most cases, but in several cadavers it was difficult to identify.

As the right crus ascends, it divides into a superficial and a deep muscle layer. The superficial layer forms the muscular rim of the right edge of the esophageal hiatus and the deep layer ascends to the left, anterior to the aorta and forms the left margin of the esophageal hiatus.

At the diaphragmatic hiatus esophagus is surrounded by the phrenoesophageal membrane, a fibroelastic ligament arising from the subdiaphragmatic fascia as a continuation of the transversal fascia lining the abdomen (Fig. 2). The upper portion of the phrenoesophageal membrane attaches one to two centimeters above the hiatus.

The outer longitudinal muscle fibres of the esophagus and the inner circular fibres are in continuation with the outer longitudinal muscle fibres of the stomach and the oblique gastric muscle fibres respectively.

The muscular wall of the cardia gradually becomes thicker because of increased density of the esophageal circular musculature on the lesser curvature and the oblique gastric musculature on the greater curvature. This line of thickness has an oblique orientation and is situated about 1.5 cm distal to the upper border of the phrenoesophageal membrane. According to Liebermann-Meffert et al (23) the lower esophageal high pressure zone corresponds to this muscular thickening and the muscular arrangement may be of importance in prevention of reflux.

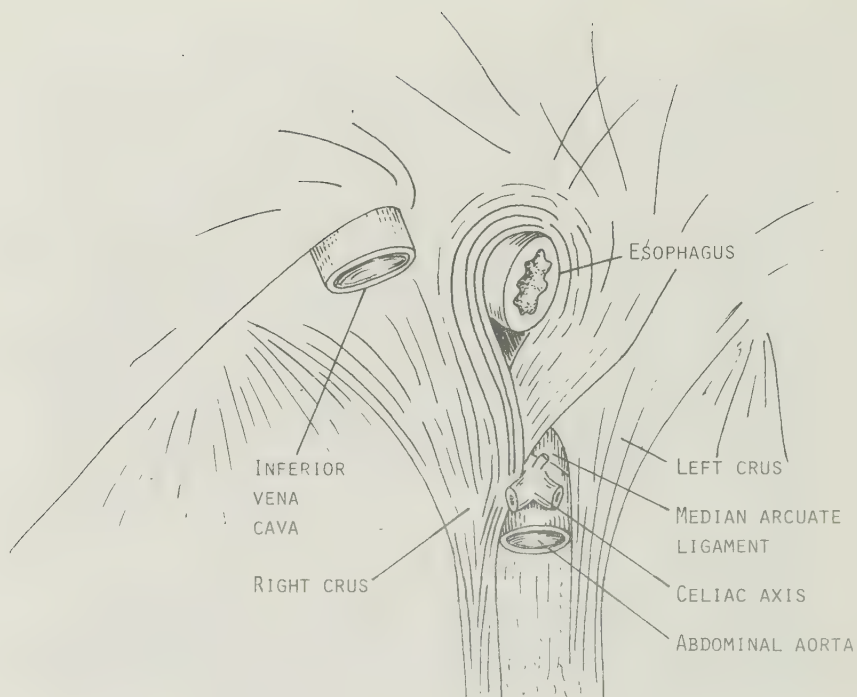


Fig. 1. Anatomy of the diaphragmatic hiatus.

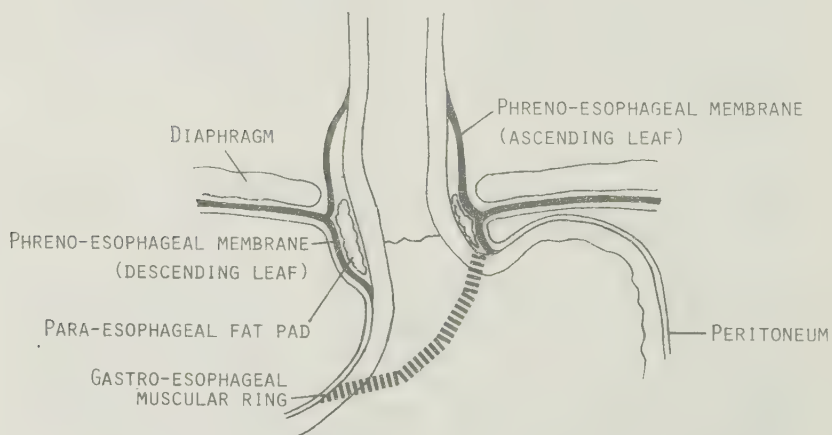


Fig. 2. Anatomy of the gastroesophageal junction.

The arterial blood flow to the lower third of the esophagus above the diaphragm comes directly from the aorta. The abdominal portion of the esophagus receives its blood supply mainly from esophageal branches of the left gastric artery.

The submucosal veins of the thoracic esophagus drain into the azygos or hemiazygos veins and the veins of the abdominal part into the coronary vein.

The lower thoracic esophagus is innervated by vagal nerves but also receives nerve fibres from the thoracic sympathetic nerve chain. Some of the postganglionic sympathetic nerve fibres reach esophagus directly and others join the vagal nerves. Vagal stimulation increases the esophageal muscle tonus and sympathetic nerve stimulation causes the opposite reaction.

Lymph vessels mainly located in the submucosa extends over a long distance in a longitudinal direction before penetrating the muscle layer and entering the lymph vessels outside the esophagus. This has the consequence that free tumour cells can follow the submucosal lymphatic plexus for a long distance before reaching regional lymph nodes. Lymphatics from the lower thoracic esophagus drain into subcarinal nodes in the inferior pulmonary ligaments but also to the nodes around the celiac axis.

PREVIOUS STUDIES

Esophagojejunal anastomoses

In spite of its controversy total gastrectomy is an established surgical procedure in the treatment of gastric carcinoma (24-26). Leakage of the subsequent esophageal anastomosis to the rest of the alimentary tract whether it is duodenum or jejunum is the main reason for postoperative morbidity and death (6, 26-28). The most simple way of reconstruction, esophagoduodenostomy has the disadvantage of a high leakage frequency (29). Schlatter (2) who is credited for the first successful total gastrectomy restored the intestinal continuity with a jejunal loop without an enterostomy. Contrary to the esophagoduodenostomy this procedure has the advantage of reducing anastomotic tension, a factor known to cause insufficiency (30). In 1929 Finney and Rienhoff (3) confirmed a better recovery rate after esophagojejunostomy than after esophagoduodenostomy. In both the reconstructions reflux esophagitis constitutes the main drawback (31).

In 1947 Orr (32) solved the problem with reflux esophagitis by performing a Roux-en-Y loop to the esophagus after total gastrectomy. By that he not only solved the problem with reflux esophagitis but he also gave us a method that reduces the frequency of leakage compared to esophagoduodenostomy. This has subsequently been confirmed (29). Not only is the esophagojejunostomy on a Roux-Y loop superior concerning leakage but it is also less dangerous if leakage occurs. Inberg (29) showed a mortality rate of 67% in leaking esophagoduodenal anastomosis but after a leaking Roux-Y esophagojejunostomy only one of thirteen patients died (8%). This difference in mortality rate is presumably due to the fact that if leakage occurs in an esophagoduodenal anastomosis pancreatic enzymes and bile will flow through the ruptured anastomosis causing a situation similar to that of a perforated ulcer and this in a patient who already has a large surgical trauma. It is shown that if the Roux-Y loop is long enough, 40 - 50 cm the duodenal content will not reach the leaking anastomosis (33).

A question that inevitably arises in connection with total gastrectomy is whether or not a gastric reservoir should be constructed. Longmire and Beal (34) reported good results after interposition of a jejunal segment. Leakage frequency was ten percent. One leakage resulted in the patients death. My major objection to interpositional surgery, particular those involving the colon, is the increased hazard of adding a detailed surgical procedure to an already extensive operation with a mortality rate between 10 - 15% also in materials published in 1985 (31, 35). Clear evidences for the benefit of gastric replacements are also lacking however. Levin (36) and Eriksson* (37) has convincingly shown that patients after a simple Roux-Y loop are

not intestinal cripples and regain their weight after six to twelve months in most instances. The weight reduction is always connected to recurrency of the tumor (36).

When operating gastric cancer patients all efforts should be directed towards complete locoregional control of the tumor and to the subsequent anastomoses. The importance of the first statement is underlined by the fact that in a series of patients operated because of recurrency of gastric carcinoma the gastric remnant and adjacent bed were the only sites of recurrent disease in 53% (38). In my opinion the most important factor influencing hospital mortality is leakage of the esophageal anastomoses, which therefor is of utmost interest to study. If the patient is in need of a reservoir it may be constructed at a later date, combined with a "second look" procedure to see that absence of recurrent cancer justifies it. In summary, the construction with a Roux-Y loop reduces strain, gives a good quality of life without disabling reflux symptoms and is quick to perform. How should the Roux-Y loop be sutured to the esophagus? End-to-end or end-to-side. End-to-end anastomoses have the advantage of diminishing the procedure to only one anastomoses compared to the end-to-side. Contrary in the end-to-side procedure the opportunity of inspecting and palpating the anastomosis is at hand. Furthermore, the circulation should be better a couple of centimeters from the cut end facilitating healing. This is pointing in direction to an end-to-side anastomosis. To perform a handsutured esophagojejunal anastomosis is time consuming and in many instances require a thoracoabdominal incision (39).

What is the role of a stapling device in construction of esophagojejunal anastomoses? Stapling devices to perform intestinal anastomoses have been used since 1826 when Denans (40) exhibited a dog ten days after he had performed an end-to-end ileoileostomy with an ingenuous apparatus. However it was not until the Russian device, PKS, for inverting end-to-end or end-to-side anastomoses of the gastrointestinal tract became available and modified in the United States (US Surgical Corporation) to the EEA-stapler as we have a reliable mechanical device for circular gastrointestinal anastomoses. Many clinical series on the use of the stapler in colonic surgery have been published (41, 42). However reports of stapled esophagojejunal anastomoses are very few and a careful long time follow up is completely lacking. The rapidity and conveniency of stapling lower colorectal anastomoses is well documented (42, 43). This is important in larger surgical procedures as in total gastrectomy, because here the surgeon must pay attention of achieving locoregional control of the tumor knowing that the subsequent anastomoses will be quickly and easily performed. The need to test stapling devices for construction of one of the most difficult gastrointestinal anastomoses, the esophagojejunostomy

is obvious. The fear for subsequent stenoses must be tested in man in careful long time follow-up studies. In a small series from 1981 Sannoke et al (44) have used the Russian SPTU stapler in fourteen esophagojejunostomies. He found one stricture and two leakages. These anastomoses were performed end-to-side. Graham et al (45) performed an end-to-side esophagojejunostomy in thirteen patients. He introduced the instrument through the subsequent enteroanastomotic site. This could be criticized because of the increased soiling in the operative field and also because the technique is impossible to use in the right thorax. Huttunen et al (46) performed an end-to-end esophagojejunostomy with the EEA-stapler in sixteen patients with leakage in two. In this series there was one failure to introduce the stapler because of a narrow bowel lumen, again elucidating the disadvantage with introducing the stapler through the enteroanastomotic site. So far, there is to the best of my knowledge, no single stapling method described which is possible to use both in the right and left thorax as well as in the abdomen. This is important because many operations for gastric carcinoma require a left or right thoracotomy in addition to the laparotomy incision. If a procedure could be used in both the left and right thorax and in the abdomen it would be of great benefit.

Numerous factors are known to influence the healing of esophageal anastomoses. Already 1929 Saint and Mann (47) held esophageal anastomoses to present greater difficulties than anastomoses elsewhere in the alimentary tract owing to its poor blood supply. Karitsky (30) also pointed out the importance of the circulation to the anastomotic ends and stressed the importance of as little strain as possible in the anastomosis. Hermreck et al (28) observed postoperative shock in five patients, four of whom subsequently had anastomotic leakage and died. This again stresses the importance of the blood supply to the anastomotic ends. The importance of avoiding tension in the anastomosis is confirmed by Kullendorf (48) who placed traction sutures in ~~several~~ ~~anastomoses~~ in the ~~stomach~~ ~~subsequently~~ found a wider anastomosis. An other factor influencing healing of the esophageal anastomosis is the lack of serosal covering. This is similar to low rectal anastomoses which are also known for a high leakage frequency (49). The fragile esophageal muscles and the constant movements of about two cm at each swallowing are other factors complicating the healing of esophageal anastomoses.

Collagen has for a long time been of a great interest in anastomotic research because it is regarded to be the dominating factor determining anastomotic strength (50 - 52). It is known that from about the fourteenth postoperative day the amount of collagen in the anastomosis is not increased (53). Still a gradual increase in breaking strength occurs for a long time (53). A worrying case report is described in 1983 where a stapled esophagojejunal anastomosis ruptured five weeks after the

operation (54). Another worrying feature of stapled colorectal anastomoses is the anastomotic narrowing (55). One of the arguments against the use of staplers is the presumption that blood flow to the anastomosis is impaired by the stapling clips. A method for measurement of blood flow to an anastomosis have however not been utilized. This would undoubtedly have been of benefit for the understanding of anastomotic healing and might have added to the development of better anastomotic techniques. In fact, there is no study evaluating the circulation in anastomoses performed either manually or stapled. The only way to achieve an objective assessment of the pro- and cons of the two techniques is to compare them in a highly standardized experimental model. This is of particular interest before advocating the use of stapled esophagojejunostomy in man and has never been done.

Lower esophageal sphincter function

The role of the lower esophageal sphincter (LES) as of the sliding hiatal hernia in the pathogenesis of reflux esophagitis has been a matter of debate. DeMeester et al (14) showed that decreased resting pressure and short intraabdominal length of LES on a population basis were a more frequent finding in patients with reflux than in patients without. Santos (56) showed that reflux occurred more frequently in patients with hiatal hernias than without, also when sphincter qualities in the two groups were equal. This study stresses the importance of the hernia itself as a determinant for gastroesophageal reflux. Pettersson et al (57) demonstrated with in vivo and in vitro experiments how the size of the hernia by influencing gastric wall tension influenced cardia competency. They found that the larger the hernia the greater the wall tension and thus the degree of incompetency. Little et al (58) demonstrated that delayed gastric emptying was a more frequent finding in patients with gastroesophageal reflux than in controls. Patients with paraesophageal hiatal hernias are also known to reflux to some extent and this in spite of a lower esophageal sphincter within the abdomen (59). These findings challenge the traditional concepts of sphincter lengths, sphincter pressure and the intra-abdominal length of the sphincter as determinants for gastroesophageal reflux. This observation has focused attention to the role of intragastric pressure, gastric dilatation and wall tension in the gastroesophageal area as determinants of gastroesophageal reflux to occur.

The etiology of paraesophageal hiatus hernia is not known. Many series confirm the fact that they are uncommon in childhood and in young adults (17, 19). This suggests that paraesophageal hiatal hernias are acquired rather than congenital in origin. Small paraesophageal hiatal hernias are very rare indicating that once the hernia formation has started it progresses rather

rapidly until nearly all of the stomach is in the chest (19). This renders the patients symptoms of epigastric fullness and distension and make them seek medical attention. The reason for the lack of small hernias can also be explained by the fact that doctors overlook early symptoms.

Thus far about 350 authentic cases of paraesophageal hiatal hernias have been documented in the literature. It is generally agreed that they represent a surgical entity and should be operated upon as soon as possible. Many series report that 30% of the patients with paraesophageal hiatal hernia present with incarceration and obstruction (17 - 19, 60). Hill (60) noticed a mortality rate of 50% in those patients where preoperative decompression was not possible.

In paraesophageal hiatal hernias an adequate length of the lower esophageal sphincter is anchored within the abdomen thereby maintaining its competency (61). On the other hand increased gastro-esophageal reflux in patients with paraesophageal hernias are observed by some surgeons in the postoperative follow-up period (19). Because a dispute exists over this issue a variety of different surgical procedures have been recommended for the repair of paraesophageal hernias. In 1968 Hill (18) proposed an anatomical repair because of an intact posterior fixation of the lower esophagus to the preaortic fascia, through an abdominal or thoracic approach. The latter was advocated as an option in incarcerated cases. Ozdemir et al (17) on the other hand favoured a left thoracotomy and a Belsey Mark IV repair because of possible disruption and laxity of the structures anchoring the cardia to the preaortic fascia. He also proposed that the dissection itself of a large hernia sac could destroy the anchoring of the lower esophagus and thus predispose for reflux. Wichterman (19) proposed the abdominal route and fixation of the stomach to the abdominal wall with a gastrostomy because two of his three patients operated through the left chest subsequently developed a volvulus. A rational elective approach seems to be through the abdomen as other disorders in the stomach like ulcers and tumors can be detected. Furthermore, the stomach can be anchored intraabdominally which prevents subsequent volvulus. In emergency operations the surgeon must be prepared for a thoracic approach because when incarceration occurs it is sometimes impossible to reduce the stomach from below.

As indicated above a most important and controversial issue concerning paraesophageal hernias is whether they reflux or not. Therefore it is astonishing that not a single study has evaluated the effect of a paraesophageal hernia on lower esophageal sphincter function. This is still more important when recognizing the fact that these hernias are generally asymptomatic until a vascular compromise occurs, causing bleeding, infarction or perforation (61). Thus the clinical presentation

of these patients does not always provide the opportunity for individual preoperative 24 h pH investigations. To provide the surgeon with better understanding of the sphincter function in patients with true paraesophageal hiatal hernias esophageal manometry and 24 h pH monitoring would be helpful.

For the surgeon the mechanical properties of the distal esophagus has so far been of most interest, whereas internists and anaesthesiologists have focused attention to its function. Morphine has a central role in pre- and postoperative periods as an analgetic drug. Stacher et al (62) studied the influence of a synthetic met-enkephalin analogue, FK 33-824, on esophageal motility in healthy humans and reported an increase in amplitude and duration of peristaltic waves in the distal one third of the esophagus. The lower esophageal sphincter was, however, not studied. For the surgeon this is more important as e.g. morphine induced incompetency of the cardia would contradict its use in the postoperative period. Therefore a study of this is of interest to perform. When performing a Hill antireflux procedure intraoperative pressure measurements of the LES are done to evaluate the effect of individual sutures. Tentatively the use of morphine may influence these measurements and therefore the results of the antireflux procedure.

Barrett's esophagus

Since 1950 when Barrett (20) described the condition of peptic ulceration in the esophagus arising in a zone of gastric type epithelium controversy has persisted concerning its etiology, complications and clinical management. Many have noticed an association between Barrett's esophagus and esophageal adenocarcinoma (21, 63 - 84). In a recent review Sjögren and Johnson (84) estimated the risk of developing adenocarcinoma in Barrett's esophagus at about ten percent. In one series 13 of 14 cases of primary esophageal adenocarcinomas in the gastroesophageal junction had residual Barrett's epithelium at this site (84). These studies can be criticized because the risk estimate is based on the prevalence of adenocarcinoma in Barrett's esophagus. To evaluate a risk of developing carcinoma, patients with Barrett's esophagus and no cancer shall be followed for a certain time and the incidence of cancer calculated and compared to general population figures for the incidence of esophageal cancer. Barrett (20) originally proposed the columnar lined esophagus to be congenital in origin. Most authorities now feel that this is an acquired lesion as the result of chronic gastroesophageal reflux (78, 85). Three different types of columnar epithelium has been described by Paull et al (86) but it is not known which of these bears the highest risk to develop carcinoma. The utmost importance of identifying this type is evident.

Naef and Savary (78) described a patient that developed a carcinoma two and a half years after a Nissen fundoplication. The authors concluded that an antireflux repair is not protection against cancer development in Barrett's esophagus. This conclusion can not be accepted because the fact that the patient is symptom free does not exclude gastroesophageal reflux (87). Furthermore, the cancer could very well be at an early stage at the time of the antireflux operation. To verify a competent antireflux repair a 24 h esophageal pH monitoring must be undertaken. So far, not a single case of benign Barrett's esophagus which has been operated upon with an effective antireflux repair has been described to develop carcinoma. The fate of the metaplastic epithelium after successful antireflux procedures is however not known. Do dysplastic changes continue towards carcinoma also after a competent antireflux repair? The importance of such a knowledge is obvious. Brand et al (88) demonstrated regeneration of squamous epithelium after antireflux repair but the biopsies were obtained with suction capsules without knowledge of the precise location of the biopsy and its relation to the squamo-columnar junction. Nor did they take into consideration the distal relocation of the gastroesophageal junction after the repairs. Heavy smoking and drinking are factors known to play a role in the etiology of esophageal carcinoma but the influence of these factors in Barrett's esophagus is not known (89). Nor is the prognosis for a carcinoma in Barrett's esophagus known compared to other esophageal carcinomas. All previous studies about Barrett's esophagus can be criticized because of a lack of a precise definition. Recognizing that the squamo-columnar junction may be irregular and that the distal one to two cm of normal tubular esophagus can be lined with cardia type columnar epithelium there is a risk that in many series of Barrett's esophagus equivocal cases are included. In my opinion a carefully documented series of a well defined population with Barrett's esophagus treated with an effective antireflux procedure would add to the understanding of which factors are of importance in the malignant degeneration of this disease.

AIMS OF THE PRESENT INVESTIGATION

1. To evaluate the eventual differences between a hand-sutured and a stapled esophagojejunostomy with respect to micro-circulation, -collagen concentration, anastomotic width, breaking strength and histology in an experimental set up.
2. To clinically assess the use of a stapler in the esophagojejunostomy after total gastrectomy.
3. To clarify the function of the cardia in the presence of a paraesophageal hiatal hernia and to resolve controversies of its management.
4. To study the relationship between factors determining the competency of the cardia.
5. To investigate the effects of therapeutic doses of morphine on distal esophageal motility and lower esophageal sphincter function.
6. To propose a precise definition of Barrett's esophagus.
7. To identify factors for malignant degeneration in Barrett's esophagus.
8. To clarify the fate and regeneration of Barrett's epithelium after antireflux surgery.
9. To compare the prognosis for patients with adenocarcinoma arising in Barrett's esophagus and for patients with other types of carcinoma in the lower esophagus.

MATERIAL

Paper I.

Thirty standard Swedish domestic female pigs weighing on an average 17.4 kg (range 13.7 - 21.2 kg) and with an age of six to eight weeks were used for the experiments. Their body weight was followed during the study. The animals were housed four per cage with free access to tap water and food (Grisex). Food, but not water, was withdrawn 24 hours before the operations and was reinstituted 48 hours afterwards.

Paper II.

During two years from November 1979 to November 1981 91 patients were treated for gastric carcinoma at the Department of Surgery in Lund. Twenty-six patients were subjected to total gastrectomy and esophagojejunostomy, 16 patients underwent a partial gastric resection and 41 patients had only minor palliative surgical procedures such as gastro-enterostomy or esophageal intubation. In the remaining eight patients non-surgical treatment was chosen. The resectability rate in the total material was 42/91 (46%). Seventeen men (median age 68, range 44-77 years) and nine women (median age 46, range 34-69 years) underwent total gastrectomy. In the material from 1970 to 1976 used for comparison and comprising 135 patients the same age distribution was at hand (median 65, range 25-81 years). The patients who underwent total gastrectomy and had a stapled esophagojejunal anastomosis were analyzed with respect to long term survival, postoperativ mortality and morbidity as well as functional results.

Paper III.

The study population consisted of 24 patients with suspicion of a paraesophageal hiatal hernia admitted to the Department of Surgery at the University of Chicago Medical Center between 1976 and 1981. Six patients were thought to have a mixed sliding and paraesophageal hernia. Of the remaining 18, 15 underwent an esophageal motility study and 24-hours esophageal pH monitoring before surgical repair. There were twelve female and six male patients. The median age was 68 years, ranging between 36 and 72.

A second study population consisted of 34 patients with sliding hiatal hernias randomly selected from those observed during the same period. The median age for these patients was 48 years (range 19-79 years) and the sex distribution 19 men and 15 women. For comparison 18 control subjects with no history or symptoms of gastroesophageal reflux, and a normal upper gastro-

intestinal radiogram at the time of voluntary inclusion into the study were used. There were eight women and ten men with a median age of 27 years ranging from 22-49 years.

Paper IV.

Gastroesophageal specimens were taken from 83 dogs. Before the removal two stitches were placed in the esophagus, one on the phrenoesophageal ligament where it attached to the esophageal wall and the other five cm above in the esophageal wall. These stitches were used to facilitate determination of the in vivo length and physiologic tension, when the specimen was placed in the in vitro model. All specimens were preserved in physiologic saline at 4°C for no more than four hours before examination in the model.

Paper V.

Fifteen healthy students, nine men and six women, age 20-27 years, median 23 years were investigated. None of them had any history of drug abuse or gastroesophageal disease. They were all participating voluntarily.

Paper VI.

Barrett's esophagus was observed in 43 patients, nine women and 34 men, in the Department of Surgery at the University of Chicago Medical Center between the years 1974 and 1982. Twenty-three patients with a median age of 55 years (range 13-78) had benign columnar epithelium lining the esophagus. In 20 patients with malignant epithelium the median age was 59.5 years (range 45-78).

METHODS

The details of the different methods used are given in the respective papers and only a short summary is given here.

Operative procedures (Papers I and II)

The pigs were operated by the same surgeon (B.W.) under general anaesthesia with the use of Pentobarbital and endotracheal intubation. All animals were artificially ventilated with nitrous oxide and oxygen. The abdomen was opened through a midline incision. After total gastrectomy the animals were randomized to either manually sutured (3-0 Dexon) or stapled (EEA, US Surgical Corporation) esophagojejunostomy end-to-side. The jejunum was cut 20 cm below the ligament of Treitz and a 40 cm Roux-en-Y loop was prepared. The controls had a laparotomy as the only surgical procedure. The EEA stapler was used according to the

manufacturer, using Prolene for the purse string suture in the cut end of the esophagus. The 25 mm cartridge was used in every pig. (Fig. 3). In the patient population (paper II) the same stapling technique was used for the end-to-side esophago-jejunosotomy but the open end of the jejunum was closed with an GIA stapling device (US Surgical Corporation). The operations were performed through abdominal incisions in 22 cases, through a left sided thoracoabdominal incision in four and in one case via a midline laparotomy incision and a separate right thoracotomy.

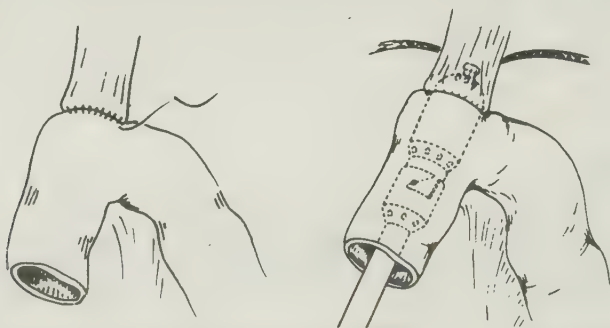


Fig. 3 After total gastrectomy and Roux-Y preparation the pigs were randomized to hand-sewn or stapled end-to-side esophagojejunal anastomoses.

The postoperative regimen differed among pigs and humans in the way that pigs were given two litres of Ringer-Glucose i.v. the first 48-hours after surgery. The patients were fed intravenously for five days after which the anastomoses were checked for leakage. If no leakage was observed the patients started to drink which was followed by a soft diet. On the seventh day a regular diet was served. A nasogastric tube was left well below the anastomosis until checked for leakage. Animals had their anastomoses checked under general anaesthesia at the seventh postoperative day. Patient endoscopy was performed the first, third, sixth, ninth and twelfth months postoperatively and every six months thereafter to check the width of the anastomosis by a measuring rod inserted through the endoscope.

The resected animals were anaesthetized one week after the gastrectomy, their body-weight measured and an X-ray performed of the esophagojejunal junction. Half of the pigs in each group were randomly sacrificed whereas the rest were observed for another four weeks and weighed once weekly.

Before sacrificing the animals by intracardial injection of saturated KCl solution microspheres were injected into the left chamber of the heart. The esophagojejunal specimen was removed in toto and examined by X-ray, which was followed by tensile tests

and blood flow measurements. Strips for histologic examination were prepared and the remaining specimens saved in a refrigerator and later examined for collagen concentration.

Radiological examinations (Paper I)

In a standard setting radiological examinations were performed in two perpendicular planes using ten percent contrast solution (Mixobar Ventrikel). From the X-ray films the inner diameters of the anastomosis and the esophagus five cm above were measured. An anastomotic index using the ratio between the two perpendicular inner diameters was calculated (fig. 4).

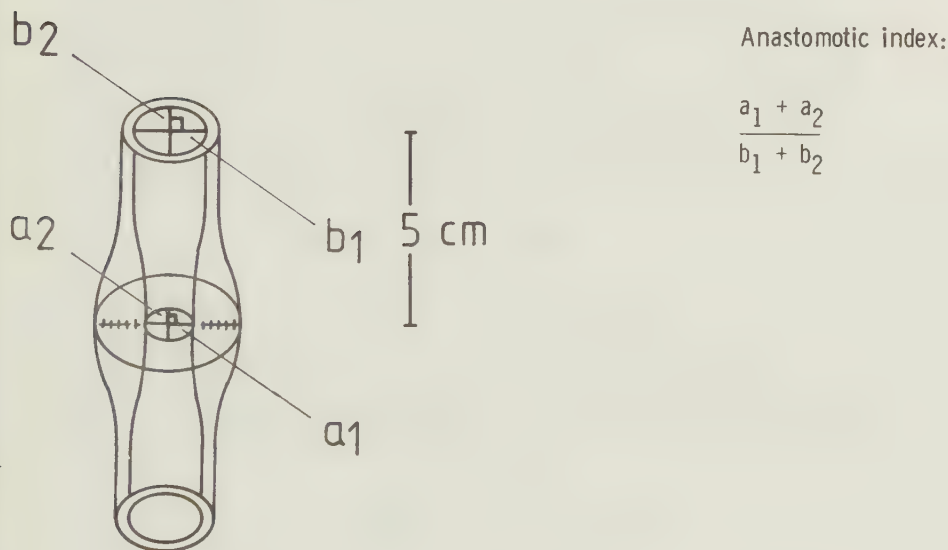


Fig. 4 The esophagojejunostomy region showing the calculation of the anastomotic index.

Tensile tests (Paper I)

Breaking strength in uni-axial tension was tested according to Löwenhielm (90) using a piezoelectric force transducer and a transient recorder. The specimen was pulled over two cylinders, one of which was attached to the stationary force transducer and the other to a pneumatic piston. The tensile force was applied at a strain rate of about ten per second.

Measurement of blood flow in the anastomotic area. (Paper I)

Measurement of specific organ blood flow was made by means of the reference organ method, described by Hafström et al (91). According to this method arterial blood flow f_i (ml $\times$ min⁻¹) in an organ (i) can be calculated using the equation:

$$f_i = \frac{q_i}{q_r} \cdot f_r$$

where f_r is the known blood flow in a reference organ. q_i and q_r is the amount of radioactivity (Bq) in the organ (i) and in the reference organ (r), respectively. The measurements are done approximately one minute after the injection of the radiolabelled microspheres into the left ventricle (Fig. 5). The use of this formula requires that the microspheres have been well mixed within the blood before leaving the heart. Assuming that the investigated organ is uniformly vascularized specific organ blood flow can be calculated from measurements of activity in an organ sample:

$$\frac{f_i}{m_i} = \frac{f_i \text{ sample}}{m_i \text{ sample}} = \frac{q_i \text{ sample}}{q_r} \cdot \frac{f_r}{m_i \text{ sample}}$$

where m_i denotes the weight of the organ (i). Cardiac output (C.O., ml $\times$ min⁻¹) can be calculated using the equation:

$$C.O. = \frac{q_{\text{tot}}}{q_r} \cdot f_r$$

where q_{tot} is the total amount of the activity injected (Bq).

In the present study $15 \pm 3 \mu\text{m}$ prelabelled nonbiodegradable ¹⁴¹Ce-microspheres in isotonic saline were used. After vigorous shaking of the syringe, the spheres were injected into the left ventricle within ten seconds. Blood was drawn into the reference organ, connected to the left femoral artery, by means of a withdrawal pump, with a flow rate of 0.6 ml/min. The collection of blood in the reference organ was started immediately before and finished two minutes after the injection of the microspheres.

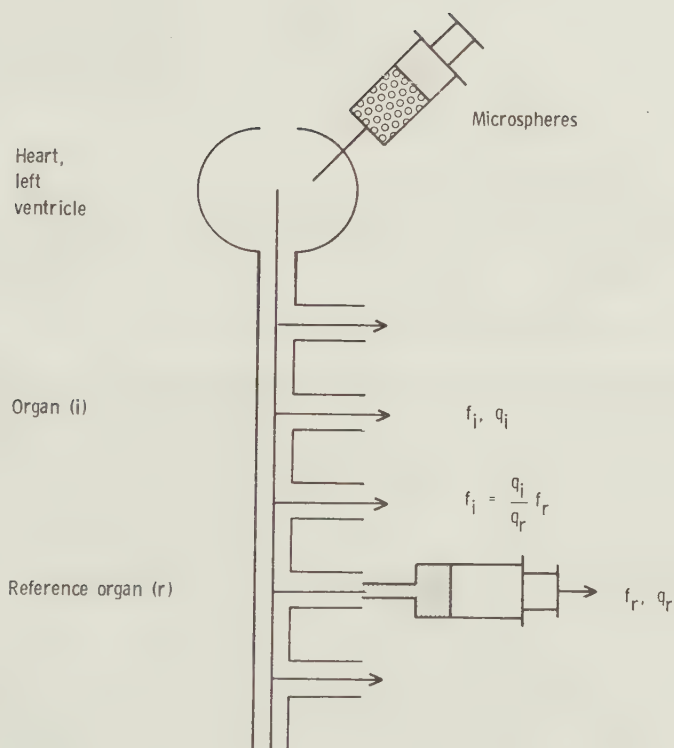


Fig. 5 Reference organ method for blood flow measurements (f_i and f_r , blood flows to the organs i and r, respectively; q_i and q_r , activities in the same organs). $15 \mu\text{m}$ large ^{141}Ce -labeled microspheres in isotonic saline solution are injected into the left ventricle.

The number of spheres used per experiment was approximately 8×10^6 (1-10 MBq), providing an error margin of less than ten percent due to fluctuations in the number of spheres. The activity of the samples was measured in a 2" x 2" well type NaI (TL) scintillation counter, corrected for counting losses and differences in sample volume. Samples were taken from the gastrointestinal tract above, nearby and below the anastomosis and from the kidneys in order to evaluate the mixing of blood and the spheres. In the control animals corresponding samples were taken from esophagus, jejunum and kidneys. Blood flow in the samples is expressed as percentage of cardiac output.

Histological examination (Paper I)

From the anastomotic area a longitudinal strip of tissue was taken for histology and stained with hematoxylin-eosine, van Gieson and McManus.

Measurements of collagen concentrations (Paper I)

Specimens weighing about 200 mg were taken from the anastomosis and segments 4-12 and 100-108 mm below and above the anastomosis. They were weighed and dried at 70°C to constant weight, usually for three days. After homogenization, collagen was extracted in distilled water and hydrolyzed in 6M HCL as described by Grant (92). The hydroxyproline content was then determined by the colorimetric method of Stegemann (93) using a Zeiss spectrophotometer. The tissue collagen concentration was estimated from its hydroxyproline contents (per cent collagen = $7.46 \times$ per cent hydroxyproline) according to Neuman and Logan (94).

Esophageal function tests (Papers III, V and VI)

Each patient (papers III and VI) was graded on a scale of 0 to 3 for symptoms of heartburn, regurgitation and dysphagia by means of a reflux questionnaire completed by one of the investigators before performance of any study. The highest obtainable score for each symptom was three, which would represent heartburn that interfered with daily activities, regurgitation associated with episodes of pulmonary aspiration and dysphagia that required hospital admission for relief of food impaction.

Esophageal manometry was performed according to the technique of Winans and Harris (95) using a single catheter assembly consisting of three fluid-filled polyethylene tubes bonded together with three two mm wide lateral openings placed five cm apart at the distal end. The catheter was passed into the stomach and withdrawn in one cm intervals into the esophagus and up to the pharynx while being perfused with sterile water by means of a pneumohydraulic capillary infusion system at a rate of 0.5 ml/min. By this technique, the location and resting pressure

of the lower esophageal sphincter (LES) and the location of the respiratory inversion point (RIP) were obtained. The sphincter pressure was measured in mm Hg as the difference between the resting end expiratory gastric pressure and sphincter pressure at the respiratory inversion point. The length of the lower esophageal sphincter below the RIP was determined by measuring the length of the distal esophageal high pressure zone affected by positive excursion associated with respiration.

Relaxation of the LES was calculated as the deflection from the basal LES pressure as indicated above and expressed as percentage of the lower esophageal sphincter pressure. Esophageal body contractions were recorded at regular intervals above RIP. Amplitude of the contractions (mm Hg) was measured from the esophageal baseline to the peak of the complexes. Duration (sec) of the contractions were measured from the upstroke of the complex to its return to the baseline.

Twenty-four hour esophageal pH monitoring was performed according to the technique previously described by Johnson and DeMeester (96). A pH electrode was placed five cm above the upper border of the lower esophageal sphincter located by manometry, and a reference lead was placed on the nondominant forearm using a method that assured good electrical contact. Both the pH probe and the reference electrode were connected through a pH meter to a strip-chart recorder running at a speed of six inches per hour for 24 hours. A normal diet was served during this period unique only in the absence of food and beverages having a pH value of less than five or more than six. Acid reflux was detected whenever the pH in the esophagus decreased to less than four. From the 24 hours recording chart the percentage of time the pH was less than four in the distal esophagus was calculated for the full 24 hours and for the upright and supine periods. In addition, the total number of reflux episodes, the number of episodes longer than five minutes, and the length of the longest reflux episode were obtained from the tracing. The normal values for the 24 hour pH test were obtained from 15 control subjects previously studied (96). The reflux status of each patient was assessed by a 24 hours pH composite score that incorporated the six components of the 24-hour recording (96).

Endoscopic examination (Papers II, III and VI)

Standard esophagogastroduodenoscopy was done with the use of a flexible fiberendoscope. With the patient resting in the left lateral position and breathing quietly, the presence of a sliding hiatal hernia was determined by observing a gastric pouch lined with rugal folds.

In the present study Barrett's esophagus is defined as a condition in which three cm or more of the distal tubular esophagus are lined by a columnar-type epithelium. This definition is deliberately chosen, recognizing that the squamo-columnar junction may be irregular, and that the distal two cm of the normal tubular esophagus are lined with a cardia-type columnar epithelium. Equivocal cases or patients with only small tongues of columnar epithelium are thereby excluded. The definition requires that three or more cm of columnar epithelium occur within the tubular esophagus, regardless of the presence or absence of a hiatal hernia. The malignant type of Barrett's esophagus is defined as the condition in which adenocarcinoma occurs above the junction of the tubular esophagus with the stomach and in which the mucosa adjacent to the carcinoma demonstrates columnar epithelium, meeting the above mentioned definition of Barrett's esophagus.

Histopathologic definitions (Paper VI)

In the columnar-lined esophagus, three distinct types of epithelium were observed. They were similar to those described by Paull et al (86). In the fundic type (FT) parietal cells and chief cells were present. The junctional or cardia type (CT) epithelium was characterized by mucous secreting columnar cells and often pyloric-type glands were present. In a third type of distinctive specialized columnar epithelium, the presence of goblet cells which sometimes contained pyloric glands indicated intestinal type metaplasia (IT).

All biopsies and resected specimens were carefully reviewed to identify dysplasia in the Barrett's epithelium. Dysplasia was defined as being "an unequivocal neoplastic alteration of the glandular (columnar-lined) esophagus". Dysplasia was graded using the criteria established for inflammatory bowel disease (Table I) (97).

TABLE 1. *Classification of Dysplasia in the Mucosa of "Barrett's" Epithelium*

Negative for dysplasia
Indefinite for dysplasia
a) Probably negative
b) Unknown
c) Probably positive
Positive for dysplasia
a) Low grade
b) High grade

The in vitro model (Paper IV)

The model used to study the relationship between esophageal tension, gastric dilatation and competency of the cardia is illustrated in figure 6. A constant pressure gastric reservoir, marked A, which could be adjusted for various levels of gastric pressure, functioned as the gastric challenge for reflux to occur. The gastroesophageal specimen was placed within an abdominal chamber connected to a second reservoir, marked B, which could be adjusted to set various levels of pressure. This pressure represents the summation of the intraabdominal and the sphincter pressures and is measured utilizing the manometer number 2. Under normal physiologic circumstances intragastric pressure is essentially equal to intraabdominal pressure; therefore any increase of intraabdominal pressure in excess of intragastric pressure can, for all technical purposes, be considered tone within the esophageal muscle, even though it was artificially produced. The distal or gastric end of the specimen was attached to an interchangeable part (marked C) of the abdominal chamber. The interchangeable parts differed from each other by varying outlet diameters of the tube that passed through it. After placement of the specimen under physiologic tension, the latter could be increased by continuous stretching of the specimen. This was achieved by sliding the tube (marked D) connected to the proximal end of the specimen in the direction out of the abdominal chamber. This movement was opposed by three metal springs within the chamber. A scale with markings for tensions corresponding to one and two kilodyne was used for adjustment of the desired tension. The length of the esophagus exposed to the abdominal pressure, (marked E), was adjusted by placing a stent, (marked F), through the esophagus, allowing only the unstented portion of it to be acted upon by the chamber pressure. Competency was determined by measuring the resistance to flow from the gastric reservoir through the specimen. This was done using the manometer number 1. Zero competency was defined as the fluid level in manometer number 1 when the whole esophagus was stented open and, therefore, no portion of it was exposed to the chamber pressure. One hundred percent competency was defined as the cessation of all flow and was indicated by a rise in the fluid level of manometer number 1 equal to the level of the gastric reservoir. Partial competency was calculated as the percentage of the rise in the fluid level in manometer number 1 between these two levels.

It is thus possible to vary all of the following parameters: overall sphincter length, sphincter pressure, intragastric pressure, intraabdominal pressure, esophageal tension and gastric outlet diameter.

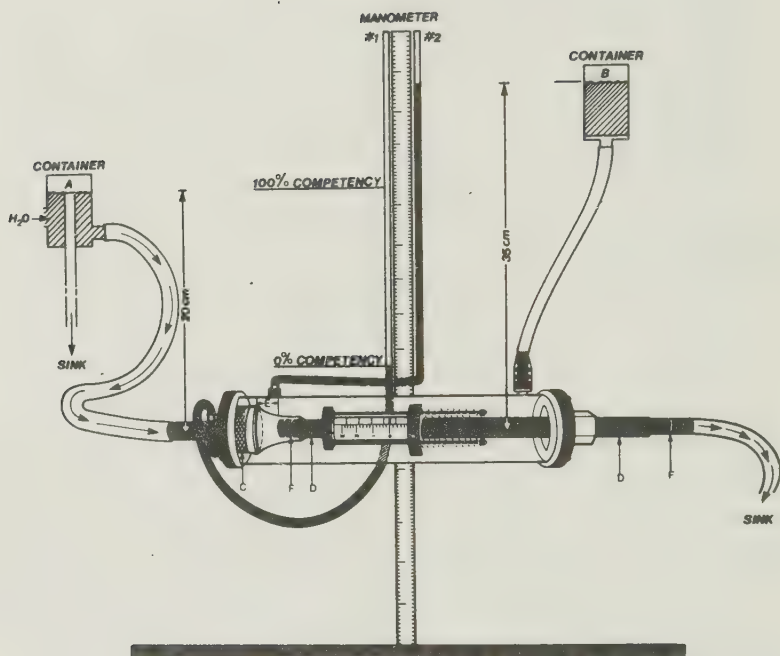


Figure 6. Schematic drawing of the model used to study the factors involved in the determination of cardiac competency. For details see Methods.

Statistical methods

The Kruskal-Wallis one-way analysis of variance by ranks was applied to test whether the samples from different groups had been drawn from the same population (98). Whenever a significance was noted, a Mann-Whitney U-test was used in order to determine whether this significance was valid also between the groups (98). In case of larger groups a normal probability plot was constructed to test whether there was a Gaussian distribution of the data (98). If so the Students t'test for unpaired data was used. If not the Mann-Whitney U-test for comparing median values was used (98). Pearson product moment correlation coefficient was used to test the association between variables (98). The Chi-square test has been used to compare frequencies when the total of the table was more than 40 (98). For smaller number Fischer's exact probability test has been applied (99). Regression analysis and linear correlation was calculated using a Minitab computer system (98).

COMMENTS ON MATERIAL AND METHODS

Experimental animals (Papers I and IV)

Growing pigs were used because their intestinal tracts were large enough to accommodate a standard stapling device. Older and larger pigs were extremely difficult to handle. In the in vitro experiment dog specimens were used because they were more accessible than pigs at the University of Chicago. Likewise the esophagus from the dog closely resembles the human esophagus.

Patients (Papers II, III, V and VI)

The patients analyzed in paper I represent a prospective series of patients referred to the Department of Surgery, Lund, for gastric carcinoma. In order to gain clinical experience of the stapling procedure in the esophagojejunal anastomosis all patients were managed in the same way. In the future a randomized study comparing manually sutured and stapled anastomoses is planned. The patients analyzed in papers III and VI represent the referral population from the University of Chicago. The racial and socio-economic pattern does not differ from the overall population in the area of the University.

The healthy control populations described in papers III and V are recruited from the students and staff at the University of Chicago, Billings Hospital. They are all volunteers and represent an equal number of men and women with an age ranging between 20 and 49 years.

Anastomotic technique (Papers I and II)

The anastomoses were made either using the stapling device according to the instruction from the manufacturer (US Surgical Corporation) or by two layers single stitches of 3-0 Dexon, which is a commonly used standard technique in gastrointestinal anastomoses. The latter is also more easy to standardize than e.g. a running sutured anastomosis.

The end-to-side technique for the esophago-jejunostomy was used after attempts on autopsy material had shown that this technique was the easiest to use. The stapling device was large enough to accommodate all tissue between the anvil and the magazine but not too large to be inserted into the esophagus. Furthermore the technique gives the opportunity to palpate and inspect the anastomosis.

Anastomotic width (Papers I and II)

The width of the anastomosis was determined after mounting the specimen as a communicating vessel and connecting it to a column of contrast with constant height. Thereby should the same pressure challenge in the anastomotic area be at hand throughout the measurements. In humans the anastomosis was measured by a

measuring rod that was 18 mm in length, i.e. the same length as the diameter of the circular knife performing the stapled anastomosis. After three months the anastomoses were in all cases wider. Because the purpose was to exclude narrowing the same measuring rod was used in all endoscopies.

Tensile tests (Paper I)

Breaking strength instead of bursting wall tension was chosen because it has been shown that from the 7th postoperative day the rupture usually occurs outside the anastomosis (100). Consequently bursting wall tension only gives limited information later (101). In the test all the suture materials were left in place because taking away staples is impossible without damaging the anastomosis. Five weeks postoperatively the Dexon sutures were completely absorbed whereas the staples were still in place.

Sampling technique (Paper I)

A double-blade cutter with eight mm between the blades was used to standardize the sampling technique. Blood flow and collagen contents was determined in anatomically defined parts. The specimens were handled within equal time periods before analysis to equalize the influence of post-mortal changes.

The microsphere technique (Paper I)

Blood flow measurements using radioactive spheres have been widely used at least for four decades. There are, however, some criteria that must be fulfilled: 1. The microspheres must be evenly distributed within the blood before leaving the heart. 2. The microspheres must be trapped in the capillaries during the first transit and no or minimal recirculation must occur. 3. The microspheres must not by themselves affect the blood flow.

An equal distribution of spheres in paired organs, for instance kidneys, can be used as an index of uniform mixing (102, 103). A correlation coefficient of 0.94 between the left and right kidneys indicates an equal distribution and uniform mixing of the spheres within the blood. The size of the spheres must not be too small, i.e. less than 10 microns, because there is a risk for them to leak through the capillary net work. Nor shall they be too large, as larger spheres tend to accumulate in the center of the blood stream (104). A size of 15 ± 3 microns seems to fulfill these criteria.

There are two techniques to inject the spheres; one through a catheter and one via direct puncture into the blood. The risk when using the catheter is that it does interfere with the blood stream through the aortic cusps. Therefore direct puncture was used. In the beginning of the experiments, the radioactivity in the lungs was measured. No activity more than expected from bronchial blood flow was detected. Also the injection site in the heart was measured for radioactivity to exclude trapping of spheres in the heart muscle, but this was ruled out.

Collagen determination (Paper I)

The collagen concentration, that is, per cent of collagen in relation to tissue dry weight was calculated because the specimens were stored in a refrigerator and the content of water could be a reason for error. In this experiment only the concentration of collagen has been measured. Presumably is the arrangement of the collagen fibrils in the anastomosis more important for the strength of the anastomosis than its collagen content and concentration.

Esophageal function tests (papers III, V and VI)

Esophageal manometry was performed under highly standardized conditions. Pope (105) has shown that non-perfused open tip catheters consistently underestimate the true pressure. Therefore a water perfused system was chosen. The perfusion rate used is shown to give accurate reproducible sphincter pressures and amplitudes of esophageal contractions (105). It is known that catheter diameter, catheter length and infusion rates will affect the pressure recordings, stressing the importance of standardization (106). All pressure measurements were made at withdrawal of the catheter (station pull through).

24-hours pH-monitoring was performed after esophageal manometry. The system was standardized at pH 4.0 and 7.0 and housed on a moveable cart. It is previously shown that 24 hour esophageal pH monitoring testing is the most objective way for determining the presence of gastroesophageal reflux in a near physiological setting (107). In addition, it allows to relate the patient's symptoms with the occurrence of reflux episodes.

The in vitro model (Paper III)

The present model is a further development of the previously used unique in vitro model (14). It gives reproducible results with the different experimental settings and is easy to handle.

RESULTS

Healing of esophago-jejunal anastomoses (Papers I and II)

The technical difficulties encountered with the manually sutured anastomosis were greatly reduced when the stapling device was used. The time for completing the anastomosis was significantly ($p<0.05$) shorter with the stapler (20 min, range 15-60 min) than with the hand-sewn technique (28 min, range 20-40 min) in the animal series. Also in man the procedure was done quickly (20 min, range 15-60min) and without difficulties. Only in one of the 27 procedures in patients did the cartridge tear the distal esophagus, resulting in a manually sutured anastomosis.

There were no major immediate complications related to the surgical procedures. One patient died 50 days after surgery in convalescence due to myocardial infarction. Three pigs died due to paraesophageal incarceration of the small intestine through the esophageal hiatus of the diaphragm.

Leakage from the anastomosis occurred in three patients. In two cases a small magazine (25 mm cartridge) was used and in the third there was a defect in the anastomotic ring. No leakage was found in the experimental series irrespective of manually or sutured anastomoses.

The actual survival curve of the patients operated upon because of gastric carcinoma with total gastrectomy did not differ from others (31, 35) (Fig. 7). One of the patients without a tumor

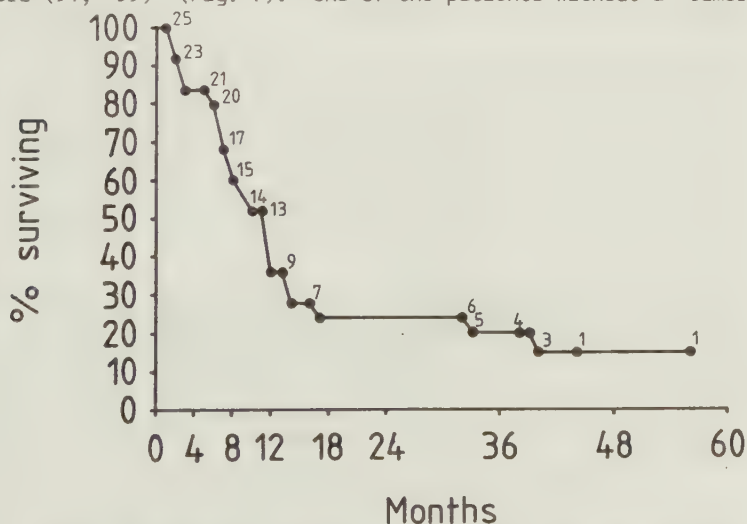


Figure 7. Actuarial survival rates after total gastrectomy and EEA esophagojejunostomy in 25 patients operated for gastric carcinoma.

free resection line developed a stricture and the other died free from dysphagia eight months postoperatively due to disseminated disease. None of these two cases leaked.

In the pigs a slight, but insignificant, decrease in anastomotic indices from one to five weeks was noticed. No difference was found between the two resected groups in this respect. In the patients, on the other hand, increasing width of the anastomoses were with time observed.

In the pigs the ultimate breaking force of the anastomoses increased with time but again no differences were found between the groups. In the pigs sacrificed after one week there was a hyperemia in the anastomotic part. Compared to controls the blood flow was significantly higher in the prompt proximal part of the anastomosis (Fig. 8). After five weeks this hyperemia has decreased (Fig. 8). At this time a significant correlation exists between small intestinal and esophageal anastomotic circulation in the prompt vicinity of the anastomosis.

Minimal alterations in collagen concentration was observed in the esophageal part of the anastomosis. This is in contrast to the intestinal part of the anastomosis, where an increase of collagen concentration takes place with time. Again there are no differences between the groups.

The role of cardia in the patophysiology of lower esophageal disorders (Papers III, IV and V)

Paraesophageal hernias and reflux (Paper III)

Paraesophageal hernias were diagnosed at a significantly higher age (68 years) than sliding hiatal hernias (48 years). In the patients with paraesophageal hernia the main symptom was dysphagia, whereas heartburn dominated the history of patients with sliding hiatal hernias. Hematemesis was found in five of the 18 patients with paraesophageal hernia but was not observed at all in patients with sliding hernia.

Seventeen of the 34 patients with sliding hernia had endoscopic evidence of esophagitis, 9 with grade I and 8 with grade II. Two of 15 with a paraesophageal hernia had grade I esophagitis and an additional three had a gastric ulcer at the point of diaphragmatic indentation of the herniated stomach. The distal stomach could be entered in only five of the 15 patients with a paraesophageal hernia, while it was easy in all patients with a sliding hernia.

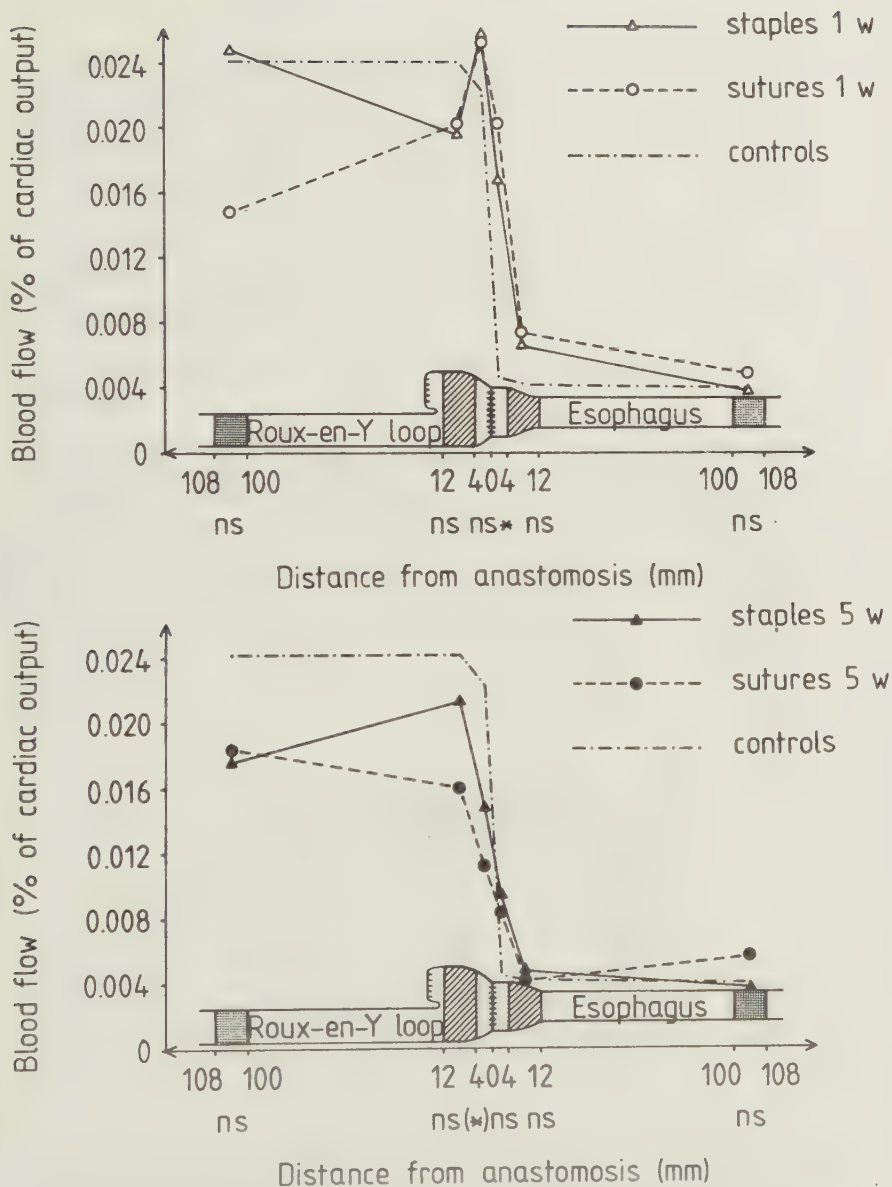


Fig. 8 Blood flow distribution (% of cardiac output) around the esophagojejunostomy after one week and five weeks. Compared to the one-week group the anastomotic circulation is diminished above all in the jejunal part ($p < 0.05^*$).

The results of 24 hour esophageal pH monitoring is shown in Fig. 9.

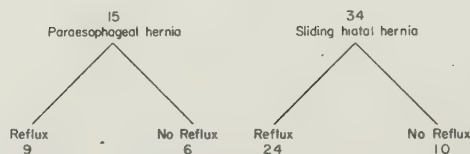


Figure 9. Results of 24 h pH monitoring in patients with paraesophageal and sliding hiatal hernias. Pathologic reflux was determined by an abnormal 24 h pH score.

There was no relation between the symptoms experienced by the patients and the competency of the cardia (Table II). With the

TABLE II Symptoms of Paraesophageal Hernia Compared With Results of 24 Hour Esophageal pH Monitoring*

Status	Positive	Negative
Heartburn	6 of 9	4 of 6
Regurgitation	6 of 9	3 of 6
Dysphagia	6 of 9	4 of 6
Postprandial fullness	8 of 9	3 of 6
Bleeding	4 of 9	1 of 6

* There was no statistical differences between the groups by Fisher's exact test.

exception of heartburn, this was also true for patients with a sliding hernia. Patients with a sliding hernia and reflux had normal length but poor tone in their sphincters and an inadequate sphincter segment exposed to the abdominal pressure. In contrast, patients with a paraesophageal hernia and reflux had a very short lower esophageal sphincter with normal tone both with virtually none of it exposed to abdominal pressure.

Patients with incompetent cardias and either paraesophageal or sliding hernia had a similar delayed clearance of acid from their esophagus as reflected in the number of reflux episodes that lasted five minutes or longer.

Mechanical factors influencing competency of the cardia (Paper IV)

Increased esophageal tension consistently resulted in decreased competency when the gastric outlet diameter and sphincter length were constant. The effects, however, of increased tension on sphincter competency was possible to reverse by increasing the sphincter length. At maximal tension of the specimen complete competency was not restored, even with a maximal (5 cm) sphincter length. In order to increase the ratio between the sphincter and intragastric pressures the sphincter pressure was gradually increased with unchanged intragastric pressure. Figure 10 illustrates how this reduces the necessary sphincter length to achieve complete competency. The slope of the curve infinitely

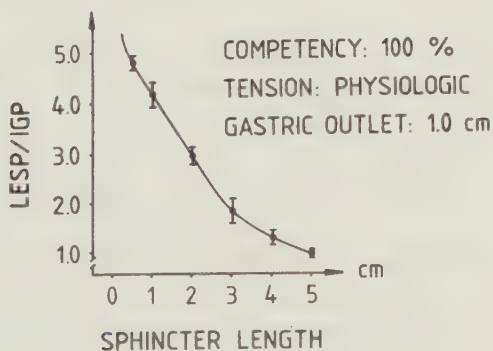


Figure 10. Interrelationship between overall sphincter length and the quotient of sphincter pressure and intragastric pressure and when complete competency was present. Gastric outlet diameter (1.0 cm) and esophageal tension (physiologic) was kept constant. Mean $\pm$ SEM.

SPHINCTER LENGTH: 2.0 cm

TENSION: PHYSIOLOGIC

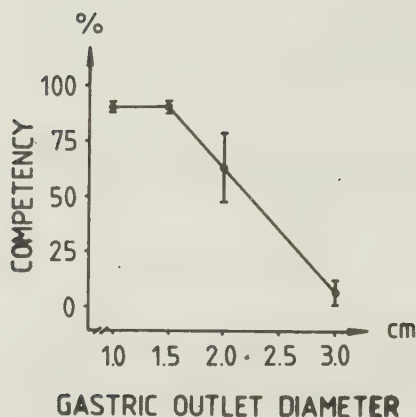


Figure 11. Relationship between gastric outlet diameter and competency of cardia when overall sphincter length (2.0 cm) and tension (physiologic) was kept constant. Mean $\pm$ SEM.

TENSION: PHYSIOLOGIC

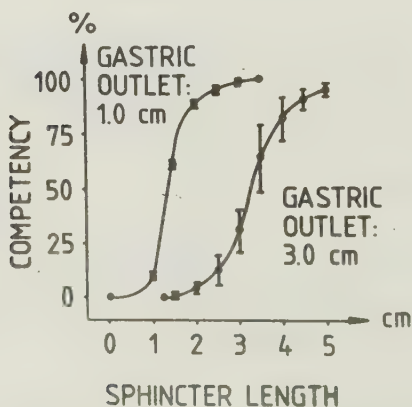


Figure 12. Effect of the overall sphincter length on competency of cardia when gastric outlet diameter was 1.0 cm and 3.0 cm respectively. Physiologic tension was applied and kept constant. Mean $\pm$ SEM.

approaches a sphincter length of zero as further increase of the ratio takes place. On the other hand is the observation that the sphincter exceeding 5.0 cm of length is unable to maintain complete competency when intragastric pressure is greater than the sphincter pressure, i.e., with a ratio less than one.

Figure 11 clearly shows how the increased gastric outlet diameter decreased competency at a constant sphincter length and physiologic tension of the specimen. With a gastroesophageal outlet diameter of one cm, complete competency was achieved when esophageal tension was physiologic and sphincter length exceeded 3.0 cm (Fig. 12). The effects of increased gastric outlet diameter were reversed by increasing the sphincter length. It was, however, not possible to completely restore full competency even with a maximal (5 cm) length (Fig. 12).

Under conditions corresponding to the physiologic situation, i.e. in vivo tension, a gastric outlet diameter of 1.0 cm and a rate of sphincter pressure over intragastric pressure exceeding 1.0, the minimal length of sphincter necessary to maintain complete competency is 3.0 cm. Decreased length consistently resulted in reduced competency unless counteracted by changes of one or several of the other factors involved.

Effects of morphine on the lower esophagus (Paper V)

Lower esophageal sphincter pressure increased slightly after subcutaneous injection of morphine. The relative relaxation of the sphincter decreased significantly with maximal effect appearing 30 minutes after the injection (Fig. 13). The amplitude of the esophageal waves increased slightly but insignificantly 10 cm above RIP in response to wet swallows but were otherwise uninfluenced. All subjects showed pupillary constriction 30-45 minutes after morphine injection, and they all experienced various degrees of light headedness and euphoria within 15 minutes and felt sleepy later on. No manometric effects were seen after saline injection.

Comparison of benign and malignant cases of Barrett's esophagus (Paper VI)

In the malignant group the incidence of smoking was greater than in the benign. Sixteen out of 20 smoked two or more packs per day. Among the male patients the correlation of smoking with malignancy was even more striking in that 16 of 18 men with cancer smoked, compared to 8 of 16 with benign Barrett's ($p < 0.025$). The drinking habits were equal in the two groups.

The relationship to gastroesophageal reflux in Barrett's esophagus was indicated by the observation that all but two of the 23 patients with benign Barrett's complained of either

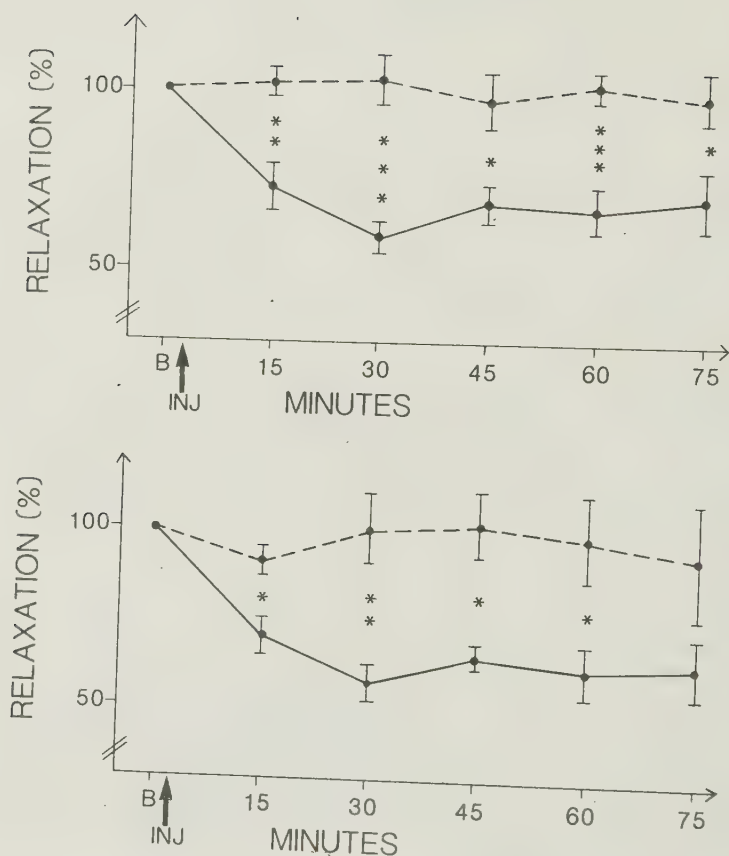


Figure 13. Lower esophageal sphincter (LES) relaxation expressed as percentage of LES pressure in response to wet swallows (Fig. 3 a) and dry swallows (Fig. 3 b) before (B) and after the injection of morphine (—) or saline (----). * denotes a p-value < 0.05, ** denotes a p-value < 0.01 and *** denotes a p-value < 0.001 when tested against basal values. Mean $\pm$ SEM.

heartburn or regurgitation. Among the malignant group 13 out of 20 complained of heartburn and/or regurgitation, but the frequency of these symptoms were significantly less ($p < 0.05$) than in the benign group.

A hiatal hernia was identified radiographically in 20 of the 23 patients with benign disease and in 16 out of 20 with malignant disease. In the latter group assessment of the hiatus could not be made in two because of the obstruction caused by the tumor. A mass or narrowing suggesting carcinoma was seen in eleven patients. Three patients having adenocarcinoma had neither a stricture nor a mass seen radiographically. Except for the presence of a bulky tumor mass in some of the malignant cases, radiologists could not differentiate with certainty between patients with Barrett's esophagus having benign or malignant epithelium. In patients without either an ulcer or a stricture, the diagnosis was frequently not made at all.

Abnormal gastroesophageal reflux was identified in 19 out of 21 patients who underwent a 24 hour pH monitoring. No significant reflux was measured by the 24 hour pH test in two patients, one of whom had had a previous vagotomy and a stricture, and another, who was referred after a successful anti-reflux repair elsewhere. The former did have abnormal reflux during the standard acid reflux test (SART). Esophageal function tests could be performed in three patients of the malignant group and documented the abnormal reflux in each. Four other patients showed free reflux on barium swallow.

All biopsies and resected specimens were carefully reviewed to identify dysplasia in the Barrett's epithelium. Among the biopsies from the 23 benign cases definite low grade dysplasia was present in two with intestinal type (IT) metaplasia. One patient was resected and a second patient refused esophagectomy and underwent a Belsey-Mark IV anti-reflux repair. Biopsies obtained seven years later showed only changes indefinite for dysplasia based upon inspection of eight biopsies.

In the malignant cases, zones of benign Barrett's epithelium were found in all resected specimens. Dysplasia of high grade was found in IT epithelium in seven specimens, low grade dysplasia in IT of nine specimens and no dysplasia in the Barrett's epithelium was noted adjacent to the adenocarcinoma in four specimens. Among the 18 patients in whom definite low grade or high grade dysplasia was at hand 16 had adenocarcinoma. In three patients undergoing esophagectomy, dysplasia, but not frank carcinoma, was found in the preoperative biopsies. Two of these patients had invasive carcinoma in the resected specimen. Dysplasia was a more serious indicator of potential malignant degeneration in Barrett's epithelium and was particularly associated with the intestinal type of epithelium.

Barrett's esophagus after anti-reflux procedures.

From the 23 benign cases, 13 patients were selected for treatment by anti-reflux repair, nine of whom had a Belsey-Mark IV procedure and four who had a Nissen fundoplication operation. Of these 13 patients, twelve have been followed today and ten have recently been restudied by esophageal function tests, radiography and esophagoscopy with multiple biopsies. These evaluations were done from two to seven years after surgery (mean four years).

Compared to preoperatively, the follow-up function tests showed a significant increase in lower esophageal sphincter pressure from a mean of 4.4 mm Hg to 12.4 mm Hg ($p < 0.01$). Length of the LES did not change significantly after the operation. Comparison of 24 h pH monitoring before and 2-7 years after anti-reflux surgery in 10 patients are seen in figure 14. Two patients were completely asymptomatic, but had abnormal frequency and duration of reflux 4 and 7 years after Belsey repairs. The SART was positive in both.

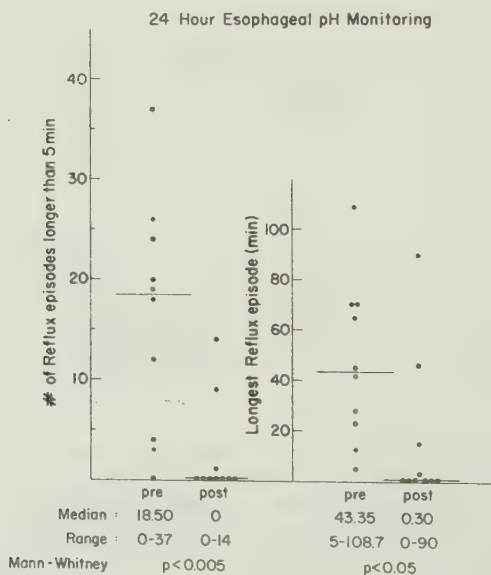


Figure 14. Comparison of measurements of reflux by 24 h pH monitoring before and 2 - 7 years after antireflux surgery in ten patients.

In eight patients the squamo-columnar junction has remained unchanged. In two, the junction was found to be four and five cm distal to the preoperative level when endoscopy was repeated within one year after the operation. These changes confirmed by biopsy were thought to be due to surgical relocation of the esophagus rather than regression of the Barrett's process. On a second postoperative endoscopy two years after the operation, no Barrett's epithelium was identified by biopsy in one of these patients. Extension of patches of squamous epithelium into regions of previously columnar line esophagus was seen in two patients. By visual endoscopic examination, this regenerating squamous epithelium appeared as distinct thin patches of opaque epithelium overlying the reddened residual columnar epithelium. This was confirmed by multiple biopsies showing normal squamous epithelium with a residual glandular epithelium beneath. In both patients, reflux had been totally corrected by Belsey Mark IV anti-reflux repairs. One patient was a non-smoker and the other had stopped smoking at the time of his anti-reflux procedure.

Four of five patients with no dysplasia preoperatively still show no dysplasia but one asymptomatic patient with a positive reflux test progressed from no dysplasia to an indefinite, probably negative, grade of dysplasia. Of the four patients with indefinite dysplasia, three have had their reflux corrected and two continue to have indefinite dysplasia and one has no dysplasia. The fourth has persistent asymptomatic reflux and has progressed to low grade dysplasia four years after surgery. On the other hand, one patient with low grade dysplasia before a successful anti-reflux repair has shown an indefinite, probably positive status, seven years later.

Four patients were selected for esophagectomy and isoperistaltic left colon interposition (108). The indications were a deep penetrating Barrett's ulcer, stricture, dysplasia, and in two previous anti-reflux repairs.

No operations were performed in six patients. In three the decision was made because of other illness and in one patient because of a previous successful Belsey Mark IV anti-reflux repair. Two patients refused operation because of minimal symptoms. In one of these, the Barrett's epithelium has progressed from an indefinite, probably negative status to high grade dysplasia during three years of observation on medical treatment. He has continued smoking, and operation has been strongly advised.

Treatment of the malignant cases with Barrett's esophagus

All 20 patients with malignant Barrett's esophagus underwent resection. In 16, a radical block resection of the mediastinum (109) was performed and in four palliative operations were

undertaken because of concomitant cardiovascular disease in two, obvious extension of disease in one and the surgeon's choice in one case. Two patients died within hospital and five additional patients died within the first six months among the 16 radically operated patients. Four patients are alive and without evident disease at nine months, two years, two and a half years and eight years. The survival curve by actuarial analysis in the patients undergoing radical esophagectomy has not varied significantly from the survival curve in 78 other patients undergoing the same operation for other types of esophageal carcinoma (Fig. 15). The four palliatively operated patients were all dead within 14 months after surgery.

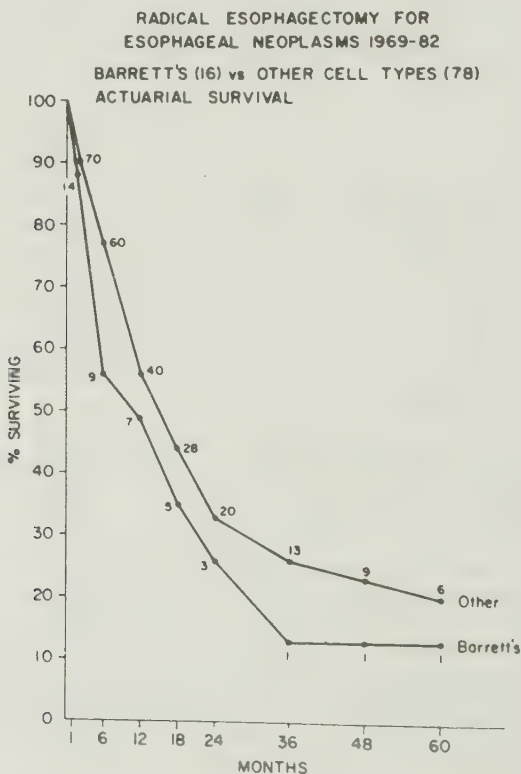


Figure 15. The survival curve by actuarial analysis in the patients undergoing radical en bloc esophagectomy for adenocarcinoma arising in Barrett's esophagus has not varied significantly from the survival curve in 78 other patients undergoing the same operation for other types of esophageal carcinoma.

DISCUSSION

Healing of esophago-jejunal anastomoses (Papers I and II)

Recognizing the poor prognosis in gastric carcinoma, and the fact that the gastric remnant and the adjacent bed were the only sites of recurrent disease in most patients operated because of recurrency, total gastrectomy including dissection of the loco-regional lymphnodes is a highly warranted procedure in the treatment of patients with gastric carcinoma (38). This is underlined by the poor long term survival rate (110). With a median survival time of eleven months as in the present series the procedure used to restore the intestinal tract should be safe and render the patient a short hospital stay. In most series there is a strong correlation between postoperative mortality and dehiscence of the esophageal anastomosis (25, 38). An important goal during these circumstances must be to find a safe reconstruction of the alimentary tract after total gastrectomy. The fastest way of performing restoration of the alimentary tract after total gastrectomy is an end-to-side esophagojejunostomy with a stapling device inserted through the open end of the jejunal loop. Many authors have questioned the value of the stapling devices (111). Probably the only way to achieve an objective assessment of the pro- and cons of newer techniques compared to older is to compare the techniques in a highly standardized experimental model. This is of particular interest before advocating the use of stapled anastomoses in man. Pigs were used in the present series because its anatomic similarity to humans. Furthermore the esophageal size in the pig was large enough to make possible the use of a standard stapling device. As was expected the operation time was shortest for the stapling device and this is similar to what is found for rectal anastomoses experimentally as well as clinically (42, 43). We found a slight anastomotic narrowing although not significantly in both the stapled and manually sutured esophagojejunostomies in the pigs. This tendency of narrowing is also true in man concerning stapled rectal anastomoses (55). In man we found a successive widening probably due to repeated dilatation caused by the passage of food.

One of the arguments against stapling devices is the presumption that blood flow to the anastomoses can be impaired by the stapling clips. To the best of my knowledge our study is the first evaluating the circulation in anastomoses performed either manually or stapled. The importance of anastomotic circulation for a good healing is well known (47). The hyperemia in the anastomotic area seen in this study both one and five weeks after resection probably reflects the metabolic demand in the healing phase and diminishes during time as the inflammatory reaction decreases. The esophagus with its low blood flow is rich in collagen. The anastomotic part increases its blood flow

more than four times in one week following the resection and approaches the high flow in the more metabolically active intestinal part. The opposite is true for the jejunal part of the anastomosis. This equalizing tendency is further underlined by the fact that after five weeks there is a significant correlation between esophageal and jejunal blood flow indicating an anastomotic scar tissue in common, being not esophageal, not jejunal but something in between. The decreased jejunal flow can in part be explained by the construction of a Roux-Y loop. No differences is noticed between the hand-sewn and stapled anastomoses one and five weeks after resection. The very early circulation is perhaps better in the stapled anastomosis because here anastomotic bleeding often is at hand and sometimes has to be stopped by a stitch..

Collagen was in this study measured by estimation of hydroxyproline which is known to be found almost exclusively in collagen (94). We expressed collagen in relation to tissue dry weight, i.e. collagen concentration, as the main purpose was to study the effect of two different suture techniques and it could be speculated that the two techniques used could cause different wall thickness and hence different amounts of tissue. In spite of difficulties in ensuring standardized biopsies there are however authors advocating determination of collagen contents instead of concentration (50). Their rationale is that an increase in collagen concentration can be due to reduction in non-collagenous components i.e. mucosal cells and muscle tissue. In experiments studying bowel rest, where a mucosal atrophy is at hand measurement of collagen content would be more accurate (112, 113). It is unlikely in our study, however, that atrophy of non-collagenous substances should be at hand, because the pigs were given food orally from the second postoperative day. There is a risk, however, that some form of atrophy is at hand in the resected group because total gastrectomy takes away one of the most important trophic hormones, namely gastrin (114). This suggestion is made stronger by the fact that the controls with the intact stomach had a lower collagen concentration in the intestinal part than the resected animals. On the other hand many studies have shown increasing collagen concentration in the anastomotic area after intestinal resection (52, 100, 101). If intestinal mucosal atrophy is a factor giving a false increase in intestinal collagen concentration at the anastomotic site then samples from other parts of jejunum should also show increased collagen concentration which was not the case.

The fact that the collagen concentration at the esophageal part of the anastomosis is unaffected by operations do not exclude the absence of gastrin as explanation for intestinal mucosal atrophy, because esophagus is known to be unaffected by gastrin (114). The hyperemia seen in both the esophageal and the jejunal part of the anastomosis is presumably reflecting the demand of nutrients

including synthesis of collagen. Collagen is known to be of importance for determination of anastomotic strength and is in the present experimental series significantly correlated to blood flow in the intestinal part of the anastomoses after one week (101). This correlation lacks in the esophageal part of the anastomoses after one week and in both parts after five weeks. It can be speculated that the anastomotic hyperemia which is not followed by increased collagen concentration in the esophagus may be one reason why leakage in esophageal anastomoses is more common than in small intestinal anastomoses. The breaking strength after one week, with the staples and sutures left in place, reflects the strength of the suture material and the tissue suture holding capacity. After five weeks the staples are still intact but the sutures absorbed. At this time the increased breaking strength, which is the same in the two groups, indicates that the dominating factor determining anastomotic strength is the fibrous tissue and not the suture material. This indicates that there is no need for sutures supporting the anastomosis after five weeks.

The series of 26 esophagojejunal anastomoses performed with the EEA-stapler in humans clearly demonstrates the role for this technique in total gastrectomy. Although our results do not differ from others (Table III) using different ways of adapting the stapler, I think that our technique of end-to-side anastomoses has many theoretical and practical advantages. The cartridge can easily be inserted through the open jejunal end and has to pass only a few centimeters before the anastomosis can be completed. Soiling of the wound is probably diminished by avoiding passage of the instrument all the way through the prepared Roux-en-Y loop when using the subsequent entero-anastomotic site for introducing the instrument (45, 46). Huttunen et al (46) showed that a narrow bowel lumen once made the passage of a stapling device impossible when the latter technique was used. Further disadvantage with the end-to-end technique is the fact that it is only possible to use in the abdomen or in the left chest through a combined thoracoabdominal incision. When the operation is performed via a laparotomy and a right thoracotomy the end-to-end technique proposed by Graham et al (45) and Huttunen et al (46) is useless, because at this stage of the operation the abdomen is closed and it is impossible to insert the stapler into the esophagus. The beneficial influence of decreasing the number of thoracoabdominal incisions, 100% in our previous series and (5/27) 18.5% in this series has to be considered, even if the comparison is made retrospectively. The reduced operating time, because of shorter time to complete the esophagojejunostomy, is probably of less importance with modern anaesthesiology but there can be economical implications for time saving procedures.

TABLE III

TOTAL GASTRECTOMY AND ESOPHAGO-JEJUNOSTOMY WITH DIFFERENT STAPLING DEVICES AND TECHNIQUES. RESULTS* OF FOUR SERIES.

MATERIALS	TECHNIQUE	TYPE OF STAPLER	FAILURE	ANASTOMOTIC LEAKAGE	STRICTURE
Y SANNOHE JAPAN 1981		SPTU	0	2/14	1
H K GRAHAM ⁺ GREAT BRITAIN 1981		SPTU EEA	1	0/13	?
B HUTTUNEN [‡] FINLAND 1982		EEA	0	2/16	1
LUND SWEDEN 1984		EEA	1	3/26	0

* NO DIFFERENCES BETWEEN GROUPS CONCERNING LEAKAGE, FAILURE OR STRICTURE FORMATION. FISHER'S EXACT PROBABILITY TEST.

⁺ X-RAY OF THE ANASTOMOSES ONLY ON CLINICAL SUSPICION OF LEAKAGE.

[‡] USUALLY REINFORCING SUTURES ALSO FASTENING THE ANASTOMOSIS TO THE DIAPHRAGM.

Leakage from the esophageal anastomosis is the main reason for early postoperative morbidity and mortality following total gastrectomy (6, 25, 29). To avoid this many ingenious techniques have been developed (see Previous studies). We prefer a stapled end-to-side Roux-Y esophagojejunostomy but also in this technique there are several crucial points. Thus the gap between the anvil and the cartridge must be large enough to accomodate the tissue. On the other hand the loading unit should be small enough to be inserted into the esophagus. In this situation one of the advantages of the end-to-side technique is obvious as the jejunal wall could be flattened and thinned, leaving enough space for the more bulky esophageal end. The 28 mm cartridge fulfilled this criteria in most instances. The three times when the 25 mm cartridge was used leakage occurred twice. Presumably the reason is that the space between that cartridge and the anvil is too small to accomodate all the tissue. The importance of intact "doughnuts" is confirmed by the fact that the only leakage, with the 28 mm cartridge occurred when one of the "doughnuts" was defect. This is also stressed by others (115). Huttunen et al (46) used reinforcing sutures and saved one cm of the most proximal part of the stomach just to facilitate the insertion of a large cartridge. This has the disadvantage of leaving part of the diseased organ, the stomach. Graham et al (45) use the end to side technique but by closing the open jejunal end prior to insertion of the stapling device through the subsequent entero-anastomotic site they miss the opportunity to palpate and inspect the esophagojejunal anastomosis. They also add the inconvenience of introducing the stapling device a long way through the intestine. There are however no differences in leakage frequency when different methods are used but the series are so far very small making conclusions difficult.

Strictures, none in this series is a serious late complication because a main goal of surgical treatment in these patients is to relieve dysphagia. West and others (115) found non-malignant strictures in four patients operated with esophagogastrostomy. The 25 mm cartridge had been used in three of these patients. In most of our patients we used the 28 mm cartridge. The passage of food may be one reason why an anastomotic widening is seen three months after surgery. An other reason may be absence of duodenal contents in the anastomotic area because of the 40 to 50 cm long Roux-Y loop. In spite of a small number of complications with the 25 mm cartridge, (2/3 leakage in the present series and 3/4 strictures in the series of West and others) we recommend the use of the largest loading-unit the esophageal lumen can accept (115).

There are, however, two risks using only staplers in esophago-jejunal anastomoses after total gastrectomy. One is illustrated by the fact that in one of our cases the anastomosis had to be

sutured by hand as the esophagus tore. Therefore diminished training in manual suturing could be fatal if not compensated for in experimental surgery. The second pitfall is the risk of leaving microscopic disease at the resection line. It is very easy to perform an abdominal esophagojejunal anastomosis with the stapling device because the need for available esophageal length is just one or two cm. This is illustrated by the fact that prior to using the stapling device for esophagojejunal anastomoses we routinely performed thoracoabdominal incisions just to be able to safely complete the anastomosis. This also gave us the opportunity to dissect another two or three cm of the esophagus and increased the chance of achieving tumor free resection lines. There is a convincing study by the British stomach cancer group indicating that the microscopic disease at the resection line influences long time survival (116). It further indicates that patients with disease in the resection line should be regarded stage IV A in the TNM staging system and considered incurable (117). The chance for cure must not be sacrificed for the convenience of avoiding a thoracotomy.

Lower esophageal sphincter function

There is a general agreement that paraesophageal hiatal hernias should be operated shortly after diagnosis to avoid life threatening complications like bleeding, infarction and perforation (61). The importance of this opinion is supported by the observation that a third of our patients experienced hematemesis. The reason for patients with paraesophageal hiatal hernias to reflux is shortening of the lower esophageal sphincter and its displacement outside the abdomen. This does not occur with sliding hernias even though they appear to be within the chest on X-ray and barium studies. The explanation for this is that a sliding hernia has a sack that functions as an extension of the abdominal cavity, whereas the paraesophageal hernia reaches the chest by an extraperitoneal route. Consequently the lower esophageal sphincter, if displaced, lies outside the abdominal cavity and is unaffected by abdominal pressure changes.

Pettersson et al (57) proposed that reflux episodes could be initiated by stretching of the lower esophageal sphincter which accompanied distention of the stomach. This could also be an explanation for paraesophageal hiatal hernia patients to reflux because in the incarcerated segment of the stomach there is an increased intragastric pressure. This secondary type of the gastroesophageal reflux, is similar to that found in patients with gastric outlet obstruction. Little et al (58) demonstrated that delayed gastric emptying was a more frequent finding in patients with gastroesophageal reflux than in controls indicating the importance of gastric dilatation. In our in vitro studies the gastric distension was reflected by different outlet diameters while intragastric pressure remained intact. This study and

others demonstrates that increasing diameter of the gastroesophageal junction impairs cardia function if not counteracted by increased length and/pressure (57). It is however inaccurate to assume that gastric dilatation reflects intragastric pressure. In the present study the relationship between intragastric pressure, sphincter pressure and competency therefore was evaluated. With a constant gastric outlet the results showed that decreased ratio of sphincter over intragastric pressure, i.e. increasing intragastric pressure, decreased competency. When intragastric pressure exceeded sphincter pressure free reflux occurred. As gastric emptying is significantly more rapid in obese patients than in non obese controls this can not be the reason why gastroesophageal reflux occurs in these patients more frequently than in non obese people (118). One explanation may be that the LES is relocated up in thorax and by that avoiding the high intraabdominal pressure.

What is the role of a hiatal hernia in the pathogenesis of reflux? It is shown that gastroesophageal reflux occurs more frequently in patients with hiatal hernias than without when their sphincter qualities are equal (56). Pettersson et al (57) showed that the larger the hernia, the greater the wall tension and the degree of incompetency. These findings are in agreement with our findings (paper IV). DeMeester et al (119) showed that decreased resting pressure and short intraabdominal length of the LES were more frequent findings in patients with hiatal hernias and reflux than in patients with hiatal hernias and no reflux indicating the importance of intraabdominal length and resting pressure of the lower esophageal sphincter.

The main objective of surgery in the treatment of gastroesophageal reflux is the reconstruction of a normal intraabdominal segment of the esophagus. Failure to control reflux in spite of this may be explained by the present findings. The advantages of increased intraabdominal sphincter length can be completely abolished if there still is tension in the gastroesophageal junction. This indicates the importance, of a meticulous dissection of esophagus ensuring a sufficient intraabdominal segment. The gastric emptying can be an other factor threatening the results of a technical perfect antireflux repair.

From a theoretical stand point the goals of antireflux procedures that have been outlined above could be achieved by a collar at the gastroesophageal junction in a way that has been attempted by Angelchik (13). What is the mode of action of this prosthesis? Samelson et al (120) concluded that it could act by interrupting distraction of the lower esophageal sphincter by gastric wall tension whereas Benjamin et al (121) suggested that the effect could be due to posterior padding of the esophago-gastric junction. Cohen et al (122) supported the view that the

mechanism of action was due to an increase in length of the lower esophageal sphincter resulting in an increased sphincter pressure when measured before and after insertion of the prosthesis. We propose that the prosthesis diminish the gastric outlet diameter and this can be the reason why it acts.

When performing antireflux repairs most surgeons look at the lower esophageal sphincter in a mechanical way. However, it must have its regulatory systems. Until recently it was assumed that the motility of the esophagus and gastroesophageal sphincter was regulated mainly by the sympathetic and parasympathetic nervous system. In addition the role in this respect of gastrointestinal hormones, especially gastrin, has been rather extensively studied. In the esophagus and lower esophageal sphincter (LES) enkephalin containing cell bodies are found abundantly (123). Five distinct types of opioid receptors have been demonstrated in the lower esophageal sphincter of opossum (124). Activation of three of these cause inhibition whereas stimulation of the remaining two results in contraction of LES. We demonstrated that subcutaneous injection of 0.2 mg morphine per kilogram body weight into healthy young adults significantly inhibited the relaxation of LES. In the distal one third of the esophagus the deglutative waves showed slight increase in magnitude but no change in duration or propagation velocity of waves between the two recording orifices situated 5 and 10 cm above the RIP. This may either be a direct influence of the morphine on smooth muscles of the distal esophagus or a compensatory response of the esophagus to overcome a non-relaxing sphincter. The inhibitory effect on LES relaxation was absent in five subjects who were injected with saline. Hall et al (125) in an earlier study demonstrated a decrease in the pressure of LES under the influence of morphine which increased the probability of gastroesophageal reflux. The divergent results of the findings in paper V when compared to others (62, 125, 126) may be explained by pharmacological differences of the administered substances. As indicated above there are opioid receptors of different qualities in LES and thus activation of these may result in stimulatory or inhibitory effects and furthermore these effects may be dose dependent. Another explanation is that somewhat different manometric techniques were used in the previous studies during which rapid pull through technique was employed. Rapid pull through is shown to have a high coefficient of variation (127). Furthermore evaluation of relaxation is impossible. The inability of LES to relax after morphine is theoretically at least very similar to a situation which is found in achalasia. It can therefore be speculated that excessive autonomous secretion of endogenous enkephalins and subsequent stimulation of specific receptors in esophagus or LES could result in some of the hitherto obscure non-specific esophageal motility disorders.

Barrett's esophagus

Since 1950 when Barrett (20) first described the condition of the peptic ulceration in the esophagus arising in a zone of gastric type epithelium increasing interest in this condition has been noticed. To permit comparison of data among various series a more precise definition is desirable. A three cm zone of columnar epithelium as we have suggested is utilized to ensure that no equivocal cases are included. Measurements of more than three cm of columnar epithelium lining the tubular esophagus is a more precise definition than the measurement of squamo-columnar junction in centimeters from the incisor teeth. (88). When the latter determination is used a large hiatal hernia may lead to proximal displacement of the squamo-columnar junction even in the absence of Barrett's epithelium. Furthermore, the distance between the incisor teeth and the squamo-columnar junction will increase after an antireflux repair.

What is the cause of Barrett's esophagus?

The high incidence of severe gastroesophageal reflux documented in the benign cases described in our study confirms many other reports and points in the direction that Barrett's esophagus is an acquired lesion (78, 85). In a report by Iascone et al (85) a greater severity of reflux in Barrett's esophagus cases are seen compared to patients with ulcerative esophagitis but without Barrett's epithelium. This indicates that the Barrett's cases have a more advanced abnormality of the cardia and acid clearance. These data adds further evidence to the likelihood that pathological reflux is a cause of Barrett's esophagus. The experimental data of Bremner, Lynch and Ellis (128) causing columnar transformation of injured esophageal mucosa further confirm that Barrett's esophagus is an acquired lesion. The report of Hamilton and Yardly (129) of Barrett's epithelium developing proximal to esophagogastric anastomoses after esophagectomy also suggests this etiology. The observations on patients developing a columnar lined esophagus after total gastrectomy and esophagojejunostomy end-to-side prove that the refluxed material must not necessarily be gastric juice (130).

The absence of symptomatic heartburn and regurgitation does not exclude pathological reflux in patients with Barrett's esophagus. Persistent severe reflux in two of our postoperative cases who were asymptomatic suggests that Barrett's epithelium may be resistant to acid. It is also wellknown that there are marked individual differences in sensitivity to reflux (87). This lack of correlation between symptoms and reflux emphasizes the importance of objective measurements of reflux in Barrett's esophagus. The importance of reflux is further underscored by the observation that dysplasia did not progress in eight patients after successful antireflux repairs. Since the two patients with continuing reflux and progressive dysplasia after antireflux

surgery were as asymptomatic as those with successful repairs the need for follow-up after surgery by pH studies is apparent. The lack of such studies may explain the occasional case reports in which carcinoma has developed at a later time following an apparently successful antireflux repair (78). So far not a single case has been described with a carcinoma developed in a columnar lined esophagus after a successful, (i.e. normal 24 h esophageal pH monitoring) antireflux repair. There is however, a highly suspicious case reported recently showing development of cancer in Barrett's esophagus after elimination of gastro-esophageal reflux (131). This patient underwent a subtotal resection of the Barrett's esophagus with a colonic interposition. After eight years the patient was readmitted because of dysphagia and was found to have a stricture at the cologastric anastomosis and adenocarcinoma in the remnant of the Barrett's esophagus. At that time a 14 h esophageal pH monitoring was undertaken and found normal. There are, however, features indicating that the patient had an abnormal gastrocoloesophageal reflux. Why did he develop a stricture at the cologastric anastomotic site without reflux of gastroduodenal (pyloroplasty) contents? This case, however, undoubtedly shows the importance of a regular check-up of patients with Barrett's esophagus also after antireflux surgery. Further, if esophagectomy is performed all of the columnar lined esophagus should be resected.

Our data suggest that the malignant degeneration of Barrett's esophagus occurs in the presence of continuing reflux and persistent smoking. The relation to smoking is never shown before but it is wellknown that smoking and drinking are important factors for developing esophageal carcinomas (89). The three patients with invasive carcinoma without a stricture or a large tumor mass studied by the pH testing showed severe reflux. Thirteen of the twenty malignant cases complained of heartburn and regurgitation and the incidence of hiatal hernia was similar to that in the benign cases. Furthermore, there was a progression to dysplasia in three patients who had continued reflux in spite of surgical or medical therapy and who continued to smoke. Two of these patients were asymptomatic and one had only minimal symptoms. This suggests that persistent reflux can lead to the development of dysplasia in the absence of symptoms, a change that seems to be potentiated by smoking. Remarkable is a finding in one patient who had low grade dysplasia. He had a successful antireflux repair and ceased to smoke. Seven years later multiple biopsies has failed to confirm progress of his dysplasia. These findings suggest that the combination of a successful antireflux repair and cessation of smoking may be effective in preventing subsequent development of dysplasia to carcinoma.

Our study does not provide a basis for judging the incidence of carcinoma in Barrett's esophagus. Other studies also suggest that Barrett's metaplasia is a usual pathway for genesis of adenocarcinoma of the lower esophagus (83). The risk of developing esophageal cancer in Barrett's esophagus has been estimated to about ten percent but this estimate is based primarily on data showing the prevalence in series of hospitalized patients (84). The only series evaluating the incidence is that of Spechler et al (132) where 115 patients treated for Barrett's esophagus between 1962 and 1983 have been followed. They found the prevalence to be seven percent and followed 105 patients with no esophageal carcinoma initially for a total of 350 person-years. Only two patients developed adenocarcinoma giving an incidence of one case per a 175 person-years. This incidence is about 40 fold greater than that of the general population but substantially lower than previously estimated. Our high prevalence of 46% is presumably higher than the overall prevalence because ours is a surgical laboratory and it can be expected that only the more symptomatic patients are those referred.

We found that adenocarcinoma were more common in men than women which is confirmed by other studies (133). We observed dysplasia in all types of epithelium (II, CI, FI) but intestinal metaplasia was present in all of our cases that developed malignancy. The type of epithelium found in Barrett's esophagus and in cases with malignant degeneration will vary depending upon whether the results are based on biopses or on resected specimen (83). These findings strongly suggest that the specialized type of intestinal metaplasia is the type most likely to undergo malignant degeneration and special observation of patients showing this type of metaplasia are suggested. No dysplasia adjacent to the carcinoma was noted in four of our 20 patients undergoing resection. This could very well be an overgrowth and replacement of precursor lesions by progressive stages of malignant transformation which is common in other neoplastic tumors like melanoma and adeno-carcinoma of the large bowel (134, 135).

Of special interest is our finding in two patients that the squamous epithelium regenerated in zones of previous Barrett's epithelium. In a previous report by Brand et al (88) the technique of demonstrating regeneration of squamous epithelium can be criticized because the biopsies are obtained with blind suction capsules without knowledge of the precise location of the biopsies and their relationship to the squamo-columnar junction. We found in two patients that squamo-columnar junction was reset distally shortly following antireflux repair and that was confirmed by early postoperative endoscopy. In those two patients the squamo-columnar junction has not changed subsequently. It may be misleading to do blind suction biopsies a couple of years after surgery because the relocation distally of

the sphincter after surgery can not be evaluated. We suggest a mechanism of squamous cell regeneration actually by replacing areas of columnar epithelium by superficial overgrowth that is clearly demonstrated in one patient. To the best of my knowledge this overgrowth of squamous epithelium has never been described before. Whether the glandular epithelium underneath will persist deep to the squamous layers, gradually atrophy and disappear completely or even persist and become malignant is unknown. If the glandular epithelium will persist deep to the squamous layers the risk for malignant degeneration must be considered higher than if the Barrett's epithelium is completely replaced by squamous epithelium.

CLINICAL CONSIDERATIONS AND FUTURE ASPECTS

Esophageal anastomoses

It is now 88 years since the first successful total gastrectomy was done (2). The mortality rate has decreased due to many factors but the - factor influencing it more than any other, leakage of the esophageal anastomosis, is the same throughout the years. In the early series collected by Finney and Rienhoff 1929 (3) and Pack and Mc Neer 1943 (136) 50 percent of deaths were due to peritonitis. Distinction between suture line leaks and peritonitis was made only rarely. In series reported 1985 (II, 31, 35) mortality rate varies between 4 - 11% and more than two-thirds of the deaths have been due to leakage of the esophageal anastomosis. The still very small series with stapled esophago-jejunal anastomoses report a hospital mortality rate of 0 - 4% and a leakage frequency of 0 - 11% (II, 44 - 46). The figures are better but the problem with leakage remain the most important issue to study.

With the development of stapling devices we have been given the unique opportunity to investigate anastomotic healing in a highly standardized fashion. If no technical difficulties arise the anastomoses should be the same every time. Future experimental works on all gastrointestinal anastomoses should concentrate on evaluating which parameters are important for a good anastomosis. This can be accomplished by defining the perfect anastomosis and evaluating which of the factors, i.e. anastomotic circulation, collagen synthesis, that best correlate to it. When knowing this factor every effort should be undertaken to optimally control it in patients.

In our study we measured the anastomotic circulation after one week and five weeks. More interesting is to follow the blood flow in the anastomotic area as a function of time. This is now although expensive possible with microspheres labelled with different radioisotopes and injected at intervals.

Collagen concentration and content is presumably of little interest for a good anastomosis. More important is to study the synthesis and structure.

Further development of stapling devices

The ideal circular stapling device for alimentary tract anastomoses should be large enough to accomodate all the tissue between the cartridge and the anvil without beeing too large to insert into a narrow lumen. When we had to use the smallest magazine (25 mm) because of a narrow esophagus we had difficulties to accomodate all the tissue between the cartridge and the anvil. This disadvantage can be altered by making a new

magazine which has a thinner central rod and also a wider gap compensated with taller staples. If this stapler was equipped with absorbable staples it could be an satisfactorily alternative to sutures. However, the importance of absorbable staples must not be insisted upon too strongly because it is more important with inert staples in the early phase of healing than early disappearance. In pigs five months after esophageal transection only 0-5 staples can be detected. Furthermore, stainless steel is not magnetic why interference with NMR not should be a problem.

Esophageal function tests.

In the vast majority of cases the esophageal laboratory is used to test whether patients have pathological gastroesophageal reflux. Thus the expensive and room consuming manometry facilities are used mainly to positioning the upper border of LES in order to correctly place the pH probe. Clinical research should pay attention to find easier ways of positioning the LES and by that giving most G P's facilities of testing patients for reflux.

Twenty-four hour esophageal pH monitoring so far the most physiological test for gastroesophageal reflux is time consuming and inconvenient for the patients. Studies of 8 h and 16 h of esophageal pH monitoring should be performed to test whether they select the same patients to reflux.

Pharmacological influence of LES.

In our study (V) we found a failure of LES to relax under influence of morphine, a situation mimicking achalasia. With further knowledge of the neurotransmitters and testing of different pharmacological agents it could be possible to elucidate some of the unresolved motor disorders like achalasia and diffuse esophageal spasm and probably develop antidotes of this disorders.

Barrett's esophagus.

Why is reflux disease important? Because, among the refluxers about 10% will develop Barrett's esophagus and this gives us an unique opportunity to detect esophageal carcinoma at an earlier stage than in most situations (133). Subsequently the patient should have a better prognosis than in the more common situation, advanced esophageal carcinoma, where curability is mere a chance. There is, however, a great deal more to be known about this fascinating entity. A better definition was asked for by Berardi and Devaiah (133), proposed by us (study VI), and found reasonable by others (137). If our definition will be the definite is questionable but an acceptable definition is the most important requirement for future work.

The reversion of columnar epithelium to squamous epithelium after successful antireflux operations demands further confirmation, because so far only a couple of cases have shown regression (88). This is important, because if regression could be shown to occur more consistently it would add a great deal to clarify the etiopathology. Furthermore if a successful antireflux repair stops progression of dysplasia we have found a cancer prophylactic operation. This also needs further confirmation, or the reverse, if a single case with a competent antireflux repair, demonstrated by a normal 24 h esophageal pH monitoring, are reported the antireflux repair cannot be considered a cancer prophylactic procedure. However, a failure can be explained by foci of early neoplasm at time of operation. Subsequently at least three years must be passed from the original operation. It is well known that in situ carcinoma of the lung can be visible to the naked eye and persist in the same phase for many years (78). An important pathway for future work is also an attempt to evaluate after how long time reversion from columnar epithelium to squamous is possible after fundoplication. Up to this date there is no report considering this question.

The mosaic of cells in Barrett's esophagus can be an effect of different reflux material. Manipulation experimentally with different intraluminal factors, bile, pancreatic juice and gastric juice could be of interest in evaluating etiology. A knowledge which of these factors are most prone to cause Barrett's esophagus is important. When these factors are identified there is a possibility for development of antidots.

There is a great need to study the true incidence of Barrett's esophagus. In a recent report (132) two patients of 105 patients followed in mean 3.3 years developed carcinoma after 5.3 years respectively 8.0 years. This indicates a more than 40-fold increased incidence of esophageal carcinoma compared to the expected incidence in the population. If this is true Barrett's esophagus is important to detect.

CONCLUSIONS

- * Except from being faster the stapled esophagojejunostomy after total gastrectomy in the pig is equal to the sutured concerning leakage frequency, anastomotic index, breaking strength, blood flow and collagen concentration one and five weeks after resection.
- * The end-to-side esophagojejunostomy constructed with the EEA-stapler inserted through the open jejunal end allows a fast, reliable anastomosis in the abdomen or in the right or left chest after total gastrectomy for gastric carcinoma.
- * Sixty percent of the patients with a paraesophageal hernia has an incompetent cardia on 24 hour pH studies which is associated with a lower esophageal sphincter of normal pressure, short overall length, and a small segment exposed to abdominal pressure. Symptoms were not helpful in determining the competency of the cardia.
- * In a unique in vitro model using gastroesophageal specimens from dogs it is clearly demonstrated that the overall sphincter length and pressure, the degree of gastric dilatation, i.e. gastric outlet diameter, the intragastric pressure and the axial tension of the esophagus are important factors in determination of cardia competency. The results also show that competency is a result of interaction between these factors and that abnormalities of one factor may be neutralized by one or several of the others.
- * Subcutaneous injection of 0.2 mg per kilogram body weight of morphine into healthy young adults inhibits the relaxation of LES. The effect is maximal after 30 minutes.
- * Dysplasia is the most serious indicator of potential malignant degeneration in Barrett's epithelium, and is particularly associated with the intestinalized type of epithelium. Smoking is more common in patients with malignant Barrett's esophagus.
- * After competent antireflux operations extension of patchy zones of squamous epithelium is seen overlying in a thin layer regions of previously columnar-lined esophagus.
- * Progress of dysplasia in Barrett's epithelium was not seen after competent antireflux operations.

- * The survival curve by actuarial analysis in patients undergoing radical en bloc esophagectomy for adenocarcinoma arising in Barrett's esophagus does not vary significantly from the survival curve in 78 other patients undergoing the same operations for other types of esophageal carcinoma.
- * The proposed definition has been accepted by others (137).

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HEALING OF THE ESOPHAGOJEJUNAL ANASTOMOSIS AFTER TOTAL GASTRECTOMY IN THE PIG

A comparative study using manually sutured or stapled anastomoses

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ABSTRACT

In the construction of esophagojejunal anastomoses after total gastrectomy the EEA stapled (US Surgical Corporation) and a two-layer interrupted 3-0 Dexon suture are compared concerning its radiological appearance, breaking strength, anastomotic circulation and collagen concentration. Thirty female pigs were used. After total gastrectomy and Roux-Y preparation the pigs were randomized to achieved sutured or stapled anastomoses.

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Ce-labeled microspheres were used for anastomotic blood flow measurements. After sacrifice the breaking strength was recorded, the collagen content determined and an anastomotic index calculated comparing two perpendicular diameters in the anastomoses and five cm above. Breaking strength, leakage frequency and anastomotic indices were the same in the two groups. One week after surgery there was a significant increase in anastomotic circulation ($p<0.05$) in both the sutured and the stapled anastomoses compared to controls. Collagen increased equal with time in the two groups ($p<0.01$). The stapled esophagojejunostomy was faster to perform (20 min) than the sutured (28 min) ($p<0.05$).

INTRODUCTION

Leakage from the esophagojejunal anastomosis after total gastrectomy is still the main reason for postoperative morbidity and death (1 - 2). Following the introduction of mechanical stapling devices encouraging results have been reported with lowered leakage frequency (3 - 6). There are, however, still no prospective, randomized series comparing the qualities of manually sutured and stapled esophagojejunal anastomoses. Factors which may influence the results of the different techniques include anastomotic blood flow and collagen metabolism. The aim of the present study is to compare stapled and manually sutured esophagojejunal anastomoses in a highly standardized experimental model. Parameters studied are the incidence of leakage and stenosis, measurement of breaking strength, blood flow and collagen concentration of the esophagojejunal specimen. Finally, a histological evaluation of the anastomotic area was performed.

MATERIAL AND METHODS

Animals

Thirty standard Swedish domestic female pigs weighing on an average 17.4 kg (range 13.7 - 21.2 kg) and with an age of six to seven weeks were used for the experiments. The animals were housed four per cage with free access to tap water and food

(Grisex). Food, but not water, was withdrawn 24 hours before the surgical procedures and was reinstituted 48 hours afterwards.

Surgical procedures

The operations were performed with the use of pentobarbital anaesthesia and endotracheal intubation. All animals were artificially ventilated with nitrous oxide and oxygen. Isotonic glucose infusion was given i.v. during the operative procedures through a jugular vein catheter. The abdominal procedures and the catheter insertion were performed under sterile conditions. An upper midline incision was used and the stomach mobilized from the greater and lesser omenta. The left and right gastric artery, the gastroepiploic artery and the short gastric vessels were ligated and divided. The stomach was removed, leaving the spleen intact. The duodenal bulb was closed with interrupted stitches in two layers, using 3-0 Dexon. The jejunum was cut 20 cm below the ligament of Treitz and a 40 cm Roux-en-Y loop was prepared. After randomization (vide infra) either a manually sutured or stapled end-to-side esophagojejunostomy was performed. The manually sutured anastomosis was done with 3-0 Dexon using a conventional 2-layer technique with interrupted stitches while holding the esophagus with an intestinal clamp (Fig 1). The open jejunal end was closed with two rows of single 3-0 Dexon stitches. The EEA stapler was used according to the manufacturer (US Surgical Corporation) using Prolene for the purse string suture in the cut end of the esophagus. After dilatation to

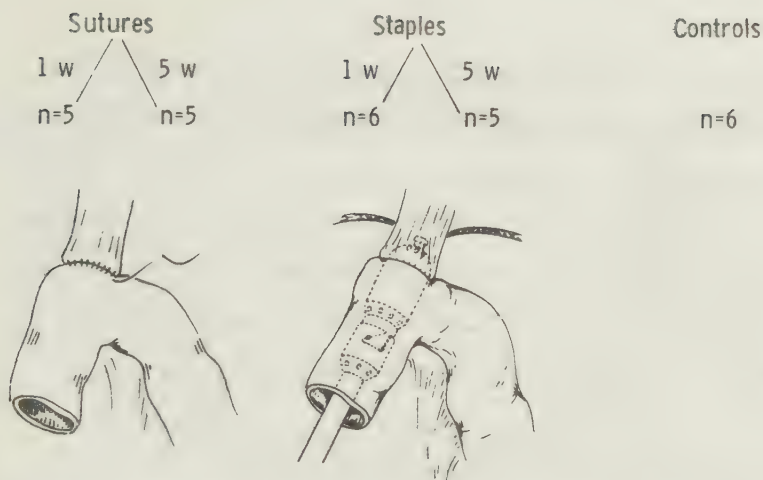


Figure 1. After total gastrectomy and Roux-Y preparation the pigs were randomized to hand-sewn or stapled end-to-side esophagojejunal anastomoses. The animals were sacrificed one or five weeks after surgery.

25 mm, the 25 mm cartridge was inserted through the open end of the jejunum and the central rod made to emerge through a scalpel incision on the antimesenteric wall five cm from the open end (Fig. 1). No purse string suture was placed around the central rod on the intestinal wall. The anvil was attached and the instrument introduced into the esophagus and the purse string suture tied (3). When firing the instrument an inverted 2-row's stapled esophagojejunostomy was accomplished with an inner diameter of 15 mm. Aside from inspection of the doughnuts and palpation of the anastomosis no intra-operative testing of the completeness of the anastomosis was performed. The open end of the jejunum was closed as described above. The time interval from the end of the preparation of the Roux loop to the end of the anastomotic completion was recorded. The jejuno-jejunal anasto-

mosis was performed end-to-side using 3-0 Dexon in two layers of interrupted stitches. The cut edges of the mesentery were approximated by a running 4-0 Dexon suture. A careful lavage of the abdominal cavity with isotonic saline was carried out and the abdomen closed with an interrupted 2-0 Dexon in the fascia and Suturamid in the skin. During the first 48 hours after surgery each pig was given 2 litres Ringer-Glucose i.v.

Experimental design

All operation were performed by the same surgeon (BW). After the abdomen was opened six animals were randomized to serve as controls. In these animals no resection was done. They were otherwise treated as the remaining 24 animals, in which the esophagojejunal anastomosis was randomly manually sutured or stapled (Fig. 1).

Seven days after surgery all animals were anaesthetized, their body weight measured and an X-ray performed of the esophagojejunal junction. Half of the pigs in each group were randomly sacrificed at this point whereas the rest were observed for another four weeks and weighed once weekly.

Before sacrificing the animals by intracardial injection of saturated KCl solution microspheres were injected. The esophagojejunal specimen was removed in toto and examined by X-ray, which was followed by tensile tests and blood flow measurements. Strips for histologic examination were prepared and the remaining specimens saved in a refrigerator and later examined for collagen contents.

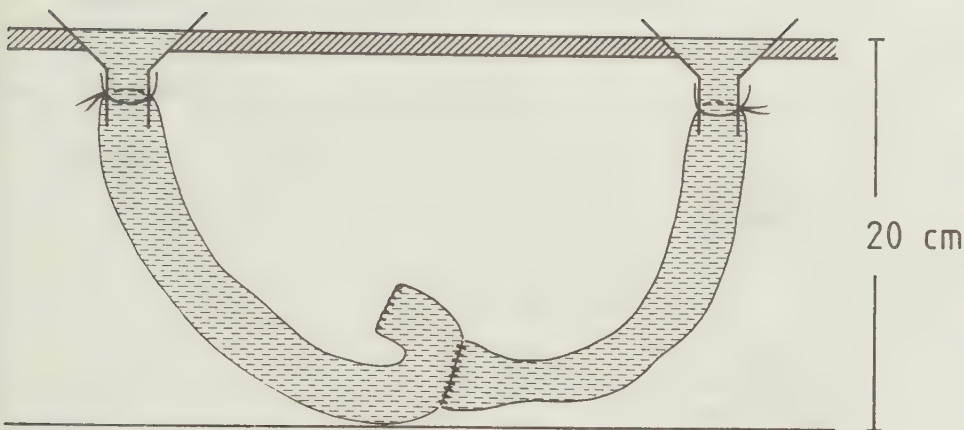
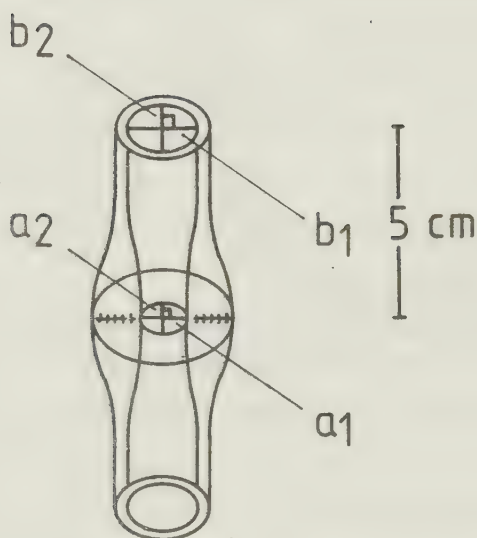


Figure 2. The standard set-up used for radiological examinations of the anastomoses.

Radiological examinations

In a standard setting radiological examinations were performed in two perpendicular planes using 10% contrast solution (Mixobar Ventrikel) (Fig. 2). From the X-ray films the inner and outer diameters of the anastomosis and of the esophagus five cm above the anastomosis were measured (Fig. 3). An anastomotic index, using the ratio between the two perpendicular inner diameters of the anastomosis and five cm above was calculated (Fig. 3). In this way any difference in diameter of the anastomosis and the esophagus was observed. A straight tube with no narrowing would obtain an index of 1.0. An anastomotic narrowing and/or a proximal dilatation results in a decreased index. Also the wall thickness in two perpendicular planes of the anastomosis was calculated.



Anastomotic index

$$\frac{a_1 + a_2}{b_1 + b_2}$$

Figure 3. The esophagojejunosomy region showing the calculations of the anastomotic index.

Tensile tests

Breaking strength in uni-axial tension was tested according to Löwenhielm (7) using a piezoelectric force transducer and a transient recorder. For this purpose the anastomotic area including five cm above and below was prepared and the test performed within two hours. The specimen was pulled over two cylinders, one of which was attached to the stationary force transducer and the other to a pneumatic piston. The specimen was tied to each cylinder by three cords. The tensile force was applied at a strain rate of about ten per second.

Measurement of blood flow in the anastomotic area

Measurement of specific organ blood flow was made by means of the reference organ method, described by Hafström et al (8). According to this method, arterial blood flow f_i (ml $\times$ min⁻¹) in an organ (i) can be calculated using the equation:

$$f_i = \frac{q_i}{q_r} \cdot f_r$$

where f_r is the known blood flow in a reference organ (r). q_i and q_r is the amount of radioactivity (Bq) in the organ i and in the reference organ r, respectively. The measurements are done approximately one minute after the injection of the radio-labelled microspheres into the left ventricle of the animal under investigation (Fig. 4). The use of this formula requires that the microspheres have been well mixed within the blood before leaving the heart. Assuming that the investigated organ is uniformly vascularized, specific organ blood flow can be calculated from measurements of activity of an organ sample:

$$\frac{f_i}{m_i} = \frac{f_i \text{ sample}}{m_i \text{ sample}} = \frac{q_i \text{ sample}}{q_r} \cdot \frac{f_r}{m_i \text{ sample}}$$

where m_i denotes the weight of the organ i.

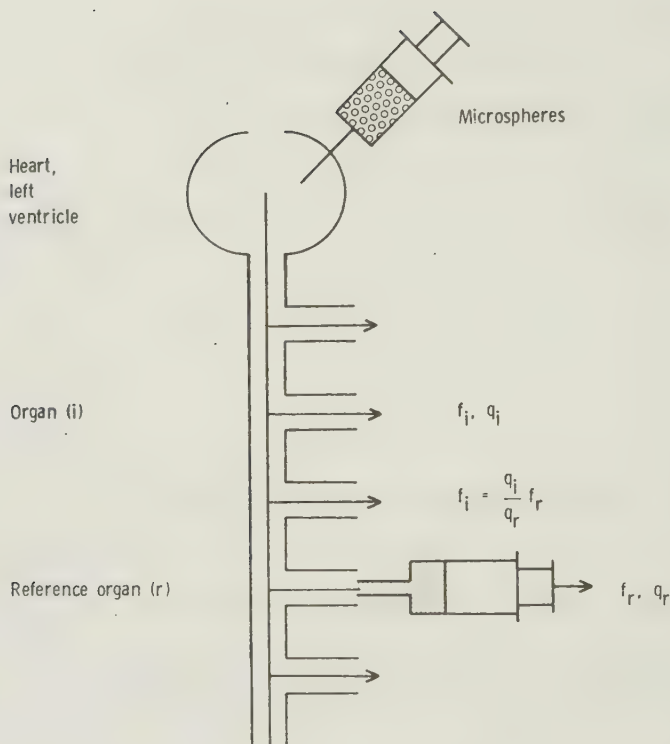


Figure 4. Reference organ method for blood flow measurements (f_i and f_r , blood flows to the organs i and r , respectively; q_i and q_r , activities in the same organs). ¹⁴¹ $^{15}\mu\text{m}$ sized Ce-labelled microspheres in isotonic saline are injected into the left ventricle.

Cardiac output (C.O., $\text{ml} \times \text{min}^{-1}$) can be calculated using the equation:

$$\text{C.O.} = \frac{q_{\text{tot}}}{q_r} \cdot f_r$$

where q_{tot} is the total amount of the activity injected (Bq).

In the present study we used $15 \pm 3 \mu\text{m}$ prelabelled non-biodegradable ^{141}Ce -microspheres in isotonic saline. After vigorous shaking of

the syringe, the spheres were injected into the left ventricle within ten seconds. Blood was drawn into the reference organ (a syringe), connected to the left femoral artery, by means of a withdrawal pump, with a flow rate of 0.6 ml/min. The collection of blood in the reference organ was started immediately before and terminated two minutes after the injection of the microspheres. The number of spheres used per experiment was approximately 8×10^6 (1-10 MBq), providing an error margin of less than ten percent due to fluctuations in the number of spheres. The activity of the samples was measured in a 2" x 2" well type NAI (TL)-scintillation counter, corrected for counting losses and differences in sample volume. Samples were taken from the gastrointestinal tract above, nearby and below the anastomosis (Fig. 5) and from the kidneys in order to evaluate the mixing of blood and the spheres. In the control animals corresponding samples were taken from esophagus and jejunum. Blood flow in the samples is expressed as percentage of cardiac output.

Determination of collagen

Specimens weighing about 200 mg were taken from the anastomosis as indicated in figure 5. They were weighed and dried at 70 °C to constant weight, usually for three days. After homogenization, collagen was extracted in distilled water and hydrolyzed in 6M HCl as described by Grant (9). The hydroxyproline content was then determined by the calorimetric method of Stegemann (10) using a Zeiss spectrophotometer. The tissue collagen concentration was estimated from its hydroxyproline content (percent collagen = $7.46 \times$ percent hydroxyproline) according to Neuman and Logan (11).

Histologic examination

From the anastomotic area a longitudinal strip of tissue was taken for histology and stained with hematoxyline-eosine, van Gieson and Mc Mann.

Statistical methods (12)

The Kruskal-Wallis one-way analysis of variance by ranks was applied to test whether the samples from the three groups had been drawn from the same population. Whenever a significant difference was noted, a Mann-Whitney U-test was used in order to determine whether this significance was valid also between the groups with sutured and stapled anastomoses. Pearson product moment correlation coefficient was used to test the association between two variables.

RESULTS

Three animals (10%) died during the first postoperative week. There was no difference among the groups in this respect. In all cases death was due to incarceration of the small intestine through a para-esophageal hiatal hernia. During the first postoperative week most animals lost weight. They reached again their preoperative weight after two weeks and then continued to gaining weight. No difficulties were obtained with any of the anastomotic techniques. The stapled anastomoses (20 min, range 15-60 min) were slightly quicker to perform than the manually sutured (28 min, range 20-40 min) ($p < 0.05$). After one week there was an incomplete mucosal bridging in one of the manually sutured anastomoses and in two of the stapled at macroscopic examination.

Radiological findings

No leakage was found. There was a slight but insignificant decrease in the anastomotic indices from one to five weeks. No differences were observed between the stapled and manually sutured groups. Furthermore, the anastomotic wall thickness one and five weeks after surgery was uninfluenced by the operative technique (Table I).

Tensile tests

The ultimate breaking force of the anastomosis increased with time. Five weeks postoperatively the anastomoses were significantly stronger compared to the situation one week postoperati-

vely. The stapled anastomoses were slightly but insignificantly stronger than the manually sutured both one and five weeks after surgery (Table II).

Table I.

Anastomotic index* and wall thickness* (mm) one and five weeks after total gastrectomy (median and IQ range).

	Anastomotic index	Wall thickness
<u>One week</u>		
Sutures	0.59 (0.49-0.63)	0.42 (0.37-0.49)
	N.S.	N.S.
Staples	0.60 (0.58-0.65)	0.38 (0.35-0.47)
<u>Five weeks</u>		
Sutures	0.51 (0.41-0.66)	0.38 (0.38-0.46)
	N.S.	N.S.
Staples	0.48 (0.35-0.65)	0.41 (0.40-0.65)

* No differences within groups from one to five weeks

Table II

Ultimate breaking force (median and IQ range) for sutured or stapled esophagojejunal anastomoses at different time intervals after total gastrectomy in the pig. Test for differences: Mann-Whitney U-test.

	Breaking force (kilopond)	
	<u>One week</u>	<u>Five weeks</u>
Sutures	13.0 (11.9-17.4)	37.0 (27.4-50.7)
	N.S.	N.S.
Staples	19.4 (16.5-23.0)	50.1 (42.0-60.8)

Blood flow measurements

For each animal the specific kidney blood flow was calculated. The correlation coefficient between left and right kidneys was 0.94, which indicates that the spheres have been well mixed within the blood.

The anastomotic blood flow was the same irrespective of the operative technique used. Significantly lower specific blood flow was noted in the esophagus when compared to the Roux loop. These findings were the same one and five weeks after the gastrectomy and in controls (Table III and Fig. 5). After one week there is a significantly higher blood flow ($p < 0.05$) in the esophageal part immediately proximal to the anastomosis, irrespective of technique used, when compared to controls. After five weeks the only difference ($p < 0.05$) occurred in the prompt distal part of the anastomosis where a lower flow in the sutured group compared to controls were found. The stapled group also had a lower flow than controls but the difference did not reach significance ($p = 0.552$). The anastomotic circulation decreased five weeks after the resection as compared to one week especially in the jejunal part ($p < 0.05$) (Table III and fig. 5). Five weeks postoperatively, a high correlation between intestinal and esophageal blood flow is at hand, which is not the case after one week. This observation was done in the resected groups (Fig. 6).

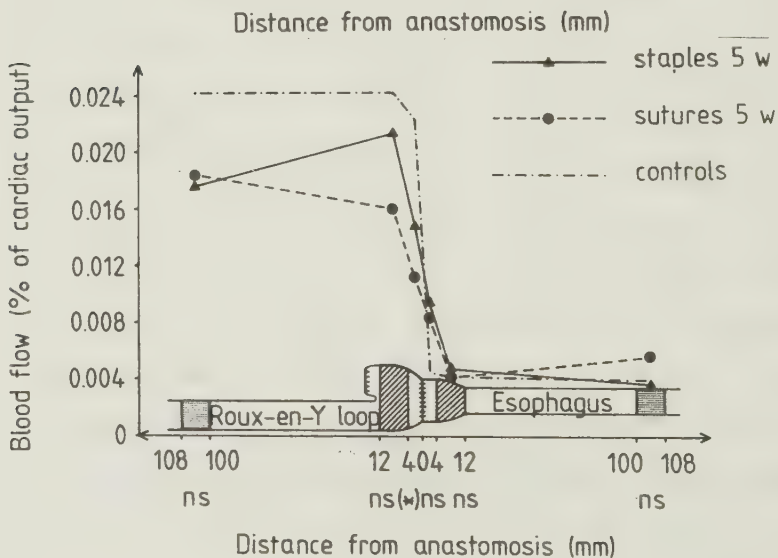
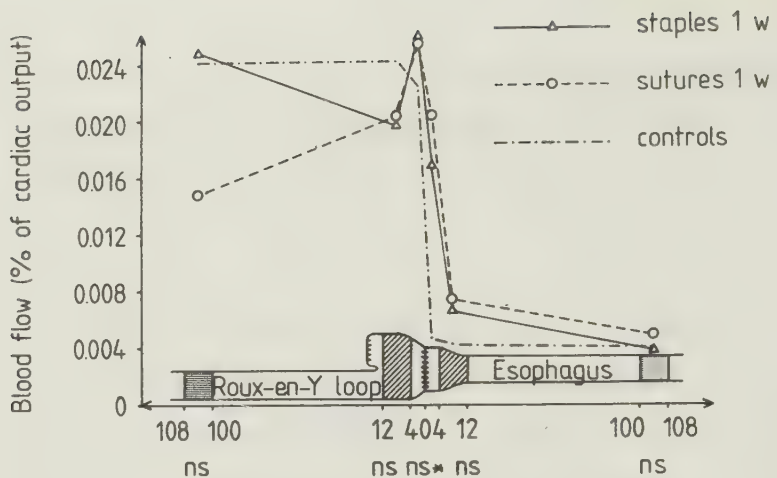


Figure 5. Blood flow distribution (% of cardiac output) around the esophagojejunostomy after one week (a) and five weeks (b). Samples were taken at different distances from the anastomosis and at corresponding sites in controls with a two blade knife at eight mm distance.

Blood flow (% of cardiac output $\times 10^{-3}$) at different distances (mm) from the esophagojejunostomy one and five weeks after total gastrectomy. Values express as median and IQ range.

	Jejunum		Anastomosis		Esophagus	
	108-100	12-4	4-0	0-4	4-12	100-108
Controls (n=6)	24 (20-33)	24 (19-29)	22 (18-33)	4,6** (3,6-5,8)	4,0 (3,0-4,9)	3,9 (2,7-8,6)
<u>One week</u>						
Sutures (n=5)	15 (10-19)	20 (16-35)	25*(17-38)	22** (13-43)	7,4 (3,5-18)	4,9 (3,9-6,7)
	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Staples (n=5)	25 (17-26)	20 (17-34)	26*(21-40)	17** (8,2-22)	6,7 (4,5-5,4)	3,8 (3,1-8,3)
<u>Five weeks</u>						
Sutures (n=5)	18 (10-27)	16 (11-23)	11*(7-16)	8,3 (4,3-11)	4,1 (2,2-6,3)	5,6 (2,5-6,7)
	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Staples (n=5)	18 (10-19)	21 (8-26)	15*(10-18)	9,3 (5,9-11,4)	4,8 (3,3-7,2)	3,4 (2,4-7,5)

* There is a significant decrease in blood flow from one to five weeks in both stapled and sutured anastomoses.

** Compared to controls the sutured and stapled anastomoses have a higher blood flow. The decrease in blood flow from one to five weeks was not significant.

Collagen

The concentration of collagen in the esophageal part of the anastomosis was uninfluenced by the operation. Contrary, in the intestinal part the collagen concentration increased following the resection. Compared to controls the collagen was significantly higher one week after the operation and still higher five weeks postoperatively ($p < 0.01$). There were no differences between the stapled or manually sutured anastomoses (Fig. 7). Furthermore, the collagen concentration of the intestine next to the anastomosis also increased significantly ($p < 0.05$) five weeks after the resection irrespective of anastomotic technique.

Microscopic appearance

It was difficult to prepare sections of high quality as the staples had to be removed before sectioning, a process that damaged the tissue. Sections from two anastomoses in the one-week manual group, from two in the five-week manual group and from three in the one-week stapled group were studied. In the one-week groups there were mucosal defects and a slight inflammatory response with predominantly round cells. The mucous gap seen in the one-week groups was overbridged after five weeks with proliferating stratified squamous epithelium, which formed a good continuity with the mucosa of the jejunum. In sections from the five-week manual group there were proliferating blood vessels and fibrous tissue at the anastomotic site and the inflammatory response had subsided.

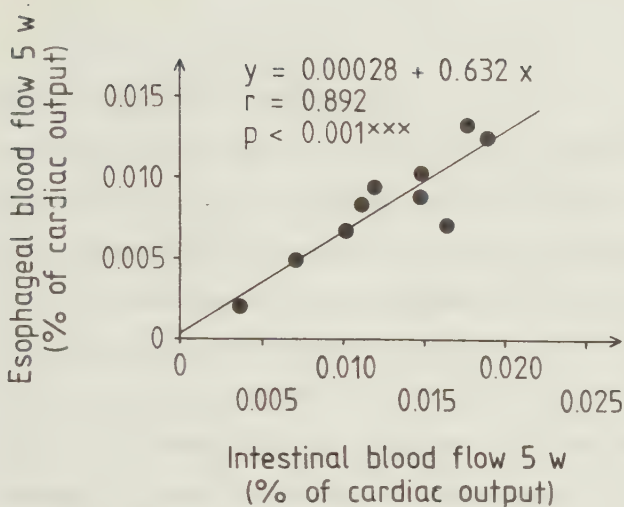


Figure 6. Regression analysis of intestinal versus esophageal blood flow (% of cardiac output) in the prompt vicinity of the anastomosis five weeks after surgery. N=10 (5 sutured + 5 stapled anastomoses).

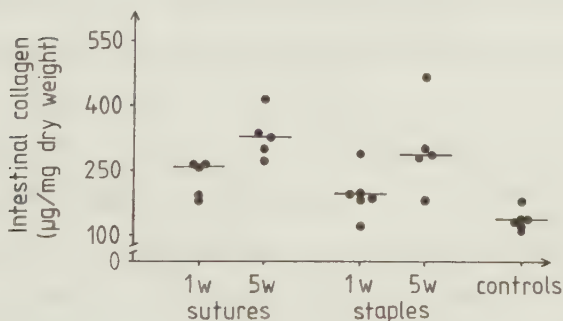


Figure 7. Collagen concentration (µg/mg dry weight) in the intestinal part of the anastomoses in controls and in resected animals one and five weeks after surgery. A significant increase in collagen concentration was observed both one and five weeks after resection compared to controls ($p < 0.05$). No difference was obtained between hand-sewn and stapled anastomoses. In the sutured group the collagen concentration increased significantly from one to five weeks ($p < 0.05$).

DISCUSSION

As previously stated, the objective of the present study was to compare the hand-sutured and the stapled esophagojejunostomy in a highly standardized experimental model. It is probably the only way to achieve an objective assessment of the pro- and cons of the two techniques. This is of a particular interest before advocating the use of stapled anastomoses in man. We prefer the pig as our experimental animal as its abdominal anatomy closely resembles the human. Furthermore, esophageal size in the pig is large enough to make possible the use of the standard stapling device.

The time for completion of the anastomoses is shortest for the stapled esophagojejunostomy and similar to what is found for rectal anastomoses experimentally (13) as well as clinically (14).

The width of the anastomosis is equal in the two groups, one and five weeks after operation, with a tendency of successive narrowing. In man, however, it is shown that this tendency is disappearing with time for both stapled rectal (15) and stapled esophagojejunal anastomoses (3). Esophagojejunal leak, none in this study, is low for all surgeons experienced with this type of anastomoses independent of technique (3-6).

One of the arguments against the use of staplers is the presumption that blood flow to the anastomoses is impaired by the stapling clips. In fact, there is no previous study evaluating the circulation in anastomoses performed either manually or stapled. In this study 15 μ m radioactively labelled microspheres are used for blood flow measurements. This technique has previously been used by one of the authors (16) in calculating anastomotic circulation. The method is known to be reliable for the gut, liver and kidney because of only small amounts of sphere shunting (17). The hyperemia in the anastomosis is presumably reflecting the metabolic demand in the healing phase and diminish during time as the inflammatory reaction decreases. This with time subsided inflammatory reaction was also confirmed by histology. In the esophagus with its low blood flow but high collagen concentration the anastomotic part increases its blood flow more than four times in one week following the resection and approaches the high flow in the more metabolically active jejunal part. Contrary the collagen content is unaffected by time. The reverse is true for the small intestine where collagen is increasing significantly while the circulation is almost unaffected. This equalizing tendency is further underlined by the fact that there is a strong correlation after five weeks between esophageal and jejunal bloodflow, i.e. with a good jejunal circulation comes a good circulation in the esophageal part of the anastomosis. This correlation lacks the first week and the anastomotic parts are obviously here more dependent of their

different origins. This scar tissue, successively achieving its own features, not esophageal, not jejunal but something in between, is equal for both the stapled and sutured anastomoses.

Collagen which is the dominating factor determining anastomotic strength (18) was in this study measured by estimation of hydroxoproline, which is known to be found almost exclusively in collagen (11). According to Neuman and Logan hydroxyproline constitutes $13.5 \pm 0.24\%$ of collagen (11). In this report we expressed collagen in relation to tissue dry weight, i.e. collagen concentration as it can be speculated that the two techniques used could result in different wall thickness. In experiments studying bowel rest, where a mucosal atrophy is at hand (19, 20), measurement of collagen content would be more accurate. In our study on the other hand there is no bowel rest as the pigs are given food orally from the second postoperative day. Therefore it is unlikely that atrophy of non-collagenous substances should be at hand. Because of total gastrectomy in the resected groups there is however one trophic hormone missing, gastrin. The controls with the stomach left has a lower collagen concentration in the intestinal part than the resected animals. This indicates that mucosal atrophy can not completely be ruled out as a factor explaining the successive intestinal increase in collagen concentration. If intestinal mucosal atrophy is a

factor bringing a false increase in intestinal collagen concentration it is astonishing that the esophageal mucosa is left intact because here the collagen is unaffected by the operation.

Saint and Mann (21) already 1929 pointed out the poor blood supply as an important reason for leaking esophageal anastomoses. The poor blood supply of the esophagus demonstrated in both controls and operated pigs is confirmed by this study (Fig. 5). In the intestinal part of the anastomosis there is a significant correlation after one week (Fig. 8) between blood flow and collagen concentration i.e. with a higher blood flow comes a higher collagen concentration. This correlation lacks in the esophageal part of the anastomoses after one week and in both parts after five weeks. Perhaps this increase of collagen is

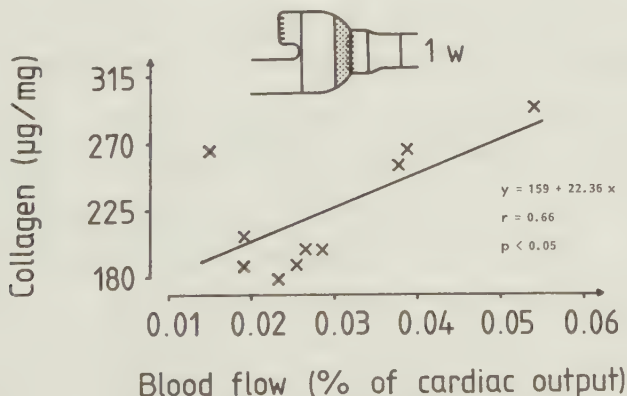


Figure 8. Regression analysis of intestinal blood flow versus collagen concentration in the anastomosis one week after total gastrectomy, $N = 10$ (5 sutured and 5 stapled anastomoses).

an effect of increased blood flow and an explanation why leakage from small intestinal anastomoses is rare. The anastomotic hyperemia also seen in the esophagus with its poor blood flow is not followed by increased collagen concentration. Consequently it can be a factor explaining the higher frequency of leakage in esophageal anastomoses.

The breaking strength after one week, with the sutures left in place, reflects the strength of the suture material and the tissue suture holding capacity. After five weeks the staples are still intact but the sutures absorbed. At this time the increased breaking strength, the same in the two groups, indicates that the dominating factor determining anastomotic strength is the fibrous tissue and not the suture material.

In conclusion; except from being faster the stapled esophago-jejunosomy after total gastrectomy in the pig is equal to the sutured concerning leakage frequency, anastomotic index, breaking strength, blood flow and collagen concentration one and five weeks after resection. Based on the results from the present study we suggest that the stapled anastomoses should be attempted also in man.

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ESOPHAGOJEJUNOSTOMY WITH THE EEA-STAPLER

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ABSTRACT

Esophagojejunostomy following total gastrectomy was attempted in 27 operations using the EEA-stapling device (US Surgical Corporation). After removal of the specimen the anastomosis is done utilizing an end-to-side technique with insertion of the cartridge and its central rod through the open jejunal end. The 28 mm wide cartridge was used in 24 anastomoses and the 25 mm wide in two. In one case the 25 mm cartridge tore the distal esophagus and the anastomosis had to be sutured manually. The median operation time was 305 minutes (range 205-560 minutes) and the time to perform the anastomosis 20 minutes (range 15-60 minutes). Anastomotic leakage occurred in three patients, of whom two were stapled with the 25 mm cartridge. They all healed with conservative treatment. One patient developed a stricture at the anastomotic site, which was due to a recurrence of the tumor. There was one hospital death. Median hospital stay was 16 days (range 8-71 days) and median survival time eleven months. It is concluded that the use of the EEA-stapler in total gastrectomy shortens the operating time, has a low complication rate and gives good functional results.

Key words: esophagojejunostomy, gastric carcinoma, stapling instruments, total gastrectomy.

INTRODUCTION

Leakage from the esophagojejunal anastomosis is the main reason for postoperative morbidity and mortality following total gastrectomy (1 - 4). The introduction of the EEA-stapling instruments offers an alternative way to perform the anastomosis which may favourably influence the results. The present paper describes operative technique and experiences with the EEA-stapler (US Surgical Corporation) in 26 consecutive patients operated on with total gastrectomy for gastric carcinoma. A previous series (5) from our department in which manually performed anastomoses were done, and three series from elsewhere, utilizing stapling devices, are used for comparison (6-8).

PATIENTS

During two years, from November 1979 to November 1981, 91 patients were treated for gastric carcinoma at the Department of Surgery, University of Lund, Lund, Sweden. Twenty-six patients were subjected to total gastrectomy and esophagojejunostomy, 16 patients underwent a partial gastric resection and 41 patients had only palliative surgical procedures such as gastroenterostomy or esophageal intubation. In the remaining eight patients non-surgical treatment was chosen due to advanced disease and bad general condition. Thus the resectability rate in the total material was 42/91 (46%). Seventeen men (median age 68, range 44-77 years) and nine women (median age 46, range 34-69 years) underwent total gastrectomy. All except one patient were

examined preoperatively by endoscopy and had biopsies verifying the diagnosis of gastric adenocarcinoma. The patient without a verified preoperative malignant diagnosis was the youngest woman in the series who was operated upon because of gastric retention thought to be a complication of duodenal ulcer disease. The location of the gastric tumors in the stomach is given in Table I. The majority of cases were confined to the cardiac region or involved all of the stomach. Twenty-two of the 26 patients had tumor growth penetrating the stomach and regional lymph node metastases were present in 19. Twenty-three patients had a low differentiated carcinoma and the pathologist judged 16 out of 26 as being of the submucous linitis-plastica type. Four patients had previously been operated with gastric resections. According to the TNM classification (9) seven were stage II, sixteen stage III and three stage IV. The localization and the stage of the tumors were the same in this and our previous series (5).

Table I

Location of the gastric tumours.

	n
Distal esophagus and cardia	7
Body	4
Antrum	4
Entire stomach	7
Gastric remnant	4
	26

METHODS

Operative procedures

In all patients total gastrectomy including splenectomy, omentectomy and dissection of the nodes around the coeliac axis and hepatoduodenal ligament was performed. An extended procedure was done in twelve patients including resection of the left colon in three, liver resection in three, resection of the pancreatic tail in four patients and bilateral salpingo-oophorectomy in five. Twenty-two of the operations were performed via a laparotomy alone, four via a left thoraco-abdominal incision and the remaining one via a laparotomy combined with a right thoracotomy. All patients were given prophylactic antibiotics (Vibramycin 200 mg i.v.). Dextran 70 (Macrodex) was used as the antithrombotic drug.

Following the removal of the specimen a retrocolic Roux-en-Y jejunal loop of 50 cm length is prepared. A purse-string suture around the cut esophagus is performed either manually by an over-and-over suture (2-0 polypropylene) or utilizing the purse-string device. When performed manually 8 - 10 bites are placed around the circumference and care is taken to enclose 2-3 mm of the entire esophageal wall in each bite.

The cartridge, without the anvil, is then inserted through the open jejunal end and the central rod made to emerge through a small scalpel incision in the antimesenteric wall five cm from the end of the loop (Fig 1 A). After attaching the anvil to the central rod the former is introduced into the esophagus and the pursestring suture tied (Fig 1 B-C). To accomplish the anastomosis in the right thorax a somewhat different technique is used. Before closing the abdominal wound the Roux-en-Y loop is temporarily attached to the specimen. Through a right-sided thoracotomy further esophageal resection is performed and the specimen removed. After division of the esophagus another two cm is dissected and angulated obliquely upwards in the wound. With the handle of the instrument outside the thoracic cavity the anastomosis is completed in the same way as in the abdomen or the left thorax. When apposing the jejunum and the esophagus by turning the wing-nut, the tissue between the anvil and the cartridge is carefully observed to avoid excessive amounts of interposed tissue (Fig 1 C-D). The inverted two layer anastomosis is completed by firing the stapler. Its inner diameter is 18 mm (the 28 mm cartridge) or 15 mm (the 25 mm cartridge). The instrument is then withdrawn by opening the wing-nut 75% of a turn and carefully rotating the instrument while pushing the jejunum upwards. Care is taken to make sure that the two "doughnuts" (i.e. the resected tissue between the central rod and the circular knife; one from the esophageal and one from the jejunal wall) are intact. The integrity of the anastomosis is

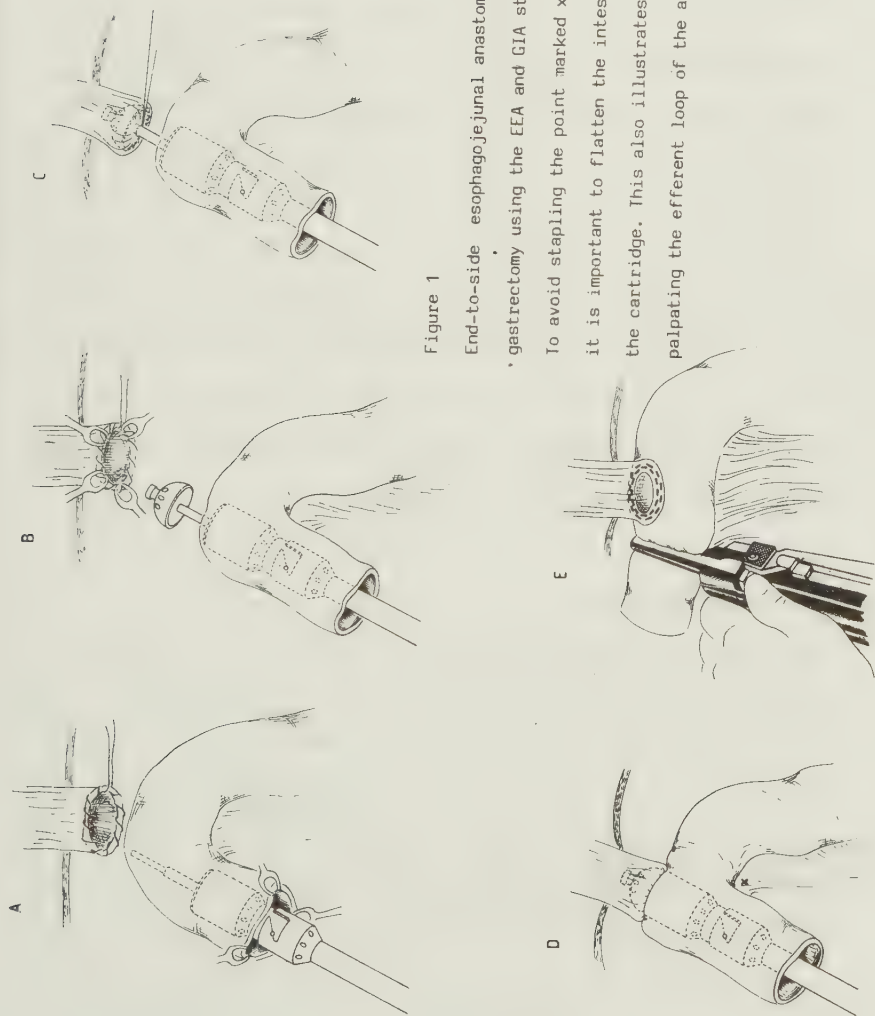


Figure 1

End-to-side esophagojejunal anastomosis after total

gastrectomy using the EEA and GIA stapling instruments.

To avoid stapling the point marked x (D) to the esophagus it is important to flatten the intestine carefully over the cartridge. This also illustrates the importance of palpating the efferent loop of the anastomosis.

tested by inserting a finger through the open jejunal end. In addition the anastomosis can be inspected using a sterile rectoscope. In the presence of intact rings the open end of the jejunal loop is closed using the GIA-instrument (US Surgical Corporation) (Fig 1 E). An outer inverted suture line with a running, absorbable 3-0 suture completes the closure of the jejunal end. If palpation or inspection of the anastomosis reveals a defect or suspicion of a defect is present, air is inflated through the nasogastric tube and the leakage located and oversewn with an absorbable 3-0 suture. The time to perform the anastomosis is measured by the anaesthesiologist (i.e. the time from the placement of the purse-string suture to the closure of the open jejunal end is completed). In order to ensure tumor clearance frozen sections of the resected margins are done per-operatively.

Postoperative regimen

The nasogastric tube is left with its tip well below the anastomosis and the patient is fed intravenously for five days after which the anastomosis is checked for leakage by x-ray using water-soluble contrast. If no leakage is observed, the patient starts to drink, which is followed by a soft diet. On the seventh day a regular diet is served and the intravenous therapy discontinued.

Follow-up

Postoperatively the patients are regularly examined by endoscopy. Photographic documentation of the anastomosis is obtained. The width of the latter is calculated by inserting a measuring rod through the biopsy channel of the endoscope. Endoscopy is performed after the first, third, sixth, ninth and twelfth months and every six months thereafter. Every patient in the series was interviewed by one of the authors with special regard to the occurrence of dysphagia.

Statistical methods

The Chi-square test has been used comparing frequencies when the total of the table was more than 40 (10). For smaller numbers Fisher's exact probability test has been applied (11). In analyzing survival the life table method was used (12).

RESULTS

Use of the EEA-stapler was attempted in 27 esophagojejunostomies, since one patient underwent a re-resection due to recurrence in the old anastomosis. One failure occurred when the insertion of the 28 mm cartridge resulted in a rupture of the esophageal wall. An attempt with the 25 mm cartridge caused another rupture and subsequently the esophagojejunostomy was performed manually. The 28 mm wide cartridge was used in 24 of the 26 stapled anastomoses and the 25 mm cartridge in the remaining two.

The median operating time was 305 minutes (range 205-560 minutes) and the median time to perform the EEA-stapled anastomosis 20 minutes (range 15-60 minutes).

Although the peroperative histologic examination revealed no tumor at the resection margins the final examination of the fixed preparation showed tumor growth at the proximal cut margin in two patients. The postoperative complications are listed in Table II. Anastomotic leakage occurred in three patients. Two of them were seen at the first postoperative fluoroscopic examination and the third on the twelfth postoperative day. Both anastomoses performed with the 25 mm cartridge leaked. The third leakage occurred in an anastomosis where the esophageal "doughnut" was incomplete. The anastomotic leakages healed after 17, 22 and 27 days respectively. They were managed non-operatively and their healing was documented fluoroscopically. Seven re-operations were done, three due to wound dehiscence, two due to postoperative bleeding, one because of intraabdominal hematoma and one due to an abscess. One patient died 50 days after the gastrectomy. His postoperative course was complicated by leakage from the esophagojejunostomy and dehiscence of the wound on the seventh postoperative day.

The median postoperative hospital stay was 16 days (range 8-71 days). Four patients are alive more than three years after the operation and the median survival time is eleven months (Fig 2).

Table II

Postoperative complications and reoperations in 26 patients undergoing 27 esophagojejunostomies.

	Number	Reoperations
Anastomotic leakage	3	0
Wound rupture	3	3
Intraabdominal abscess	2	1
Empyema	1	0
Wound infection	1	0
Intraabdominal hematoma	1	1
Postoperative bleeding	2	2
	13	7

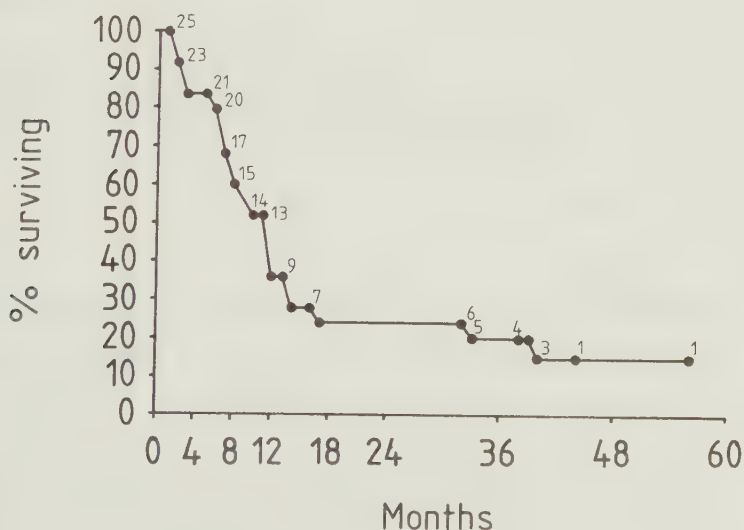


Figure 2

Actuarial survival rates after total gastrectomy and EFA esophagojejunostomy in 25 patients operated for gastric carcinoma.

At endoscopic examination three months after the operation the diameter of the anastomosis was more than 18 mm even in the patients where the 25 mm cartridge had been used. One patient complained of dysphagia including an episode of meat impaction requiring clearing with liquids. He had a recurrence in the anastomotic site.

DISCUSSION

The present series of 26 esophagojejunal anastomoses performed with the EEA-stapler clearly demonstrates that there is a role for this procedure in total gastrectomy. The incidence of severe complications such as anastomotic leakage and hospital mortality is lower compared to previous series from our department (Table III). Furthermore anastomotic strictures were absent except in one case, the patient with recurrence of the tumor at the anastomotic site.

Since its introduction in the United States the EEA-stapler has been successfully used in low anterior colo-rectal resections (13-15) and tried in esophageal surgery (16, 17). The unsatisfactory results generally reported on the quality of the hand sewn esophagojejunal anastomosis following total gastrectomy encouraged us to attempt to use the stapling-device in this operation. After training in the procedure in cadavers and later in pigs (18) the end-to-side technique was chosen. Although our

results do not differ from others using different ways of adapting the stapler (Table IV) we think the end-to-side anastomosis has many theoretical and practical advantages. The cartridge can easily be inserted through the open jejunal end and has to pass only a few centimeters before the anastomosis can be completed. Soiling of the wound is probably diminished by avoiding passage of the instrument all the way through the prepared Roux-en-Y loop when using the subsequent entero-anastomotic site for introducing the instrument (7, 8). In addition a narrow bowel lumen may make the passage difficult or even impossible when the latter technique is used (8).

Table III

Hospital mortality and incidence of anastomotic leakage in two series of total gastrectomy from our department.

Time period	<u>1970-1975</u>		<u>1979-1981</u>
Anastomotic technique	Manual*		Stapling device
Anastomotic leakage	25/135 (18,5%)	NS	3/26 (11,5%)
Hospital mortality	13/135 (9,6%)	NS	1/26 (3,9%)

* The anastomosis was made end-to-end with two rows of single 3-0 absorbable stitches.

When the operation has to be performed via a right thoracotomy the anastomosis can be completed by dissecting free two cm of the distal esophagus and obliquely directing the instrument through the open jejunal end into the esophagus. It is not possible to do this with the techniques used by Graham et al (7) and Huttonen et al (8) because at this stage of the operation the abdomen is closed. Contrary to previous series (5) using hand sewn esophago-jejunal anastomoses the number of thoraco-abdominal incisions (100%) was significantly reduced. The beneficial influence of this on the postoperative morbidity in this series (5/27, 18.5%) and mortality has to be considered even if comparison is made retrospectively. The reduced operating time, because of shorter time to complete the esophagojejunosomy, is probably of less importance with modern anaesthesiology. The economical implications of time saving procedures should, be considered.

Leakage rate from the esophagojejunal anastomosis is low in series using staplers (Table III and IV). These data should, however, be cautiously interpreted since the series utilizing staplers hitherto are small and generally done by specially interested surgeons. Furthermore there is still a lack of prospective, randomized studies comparing the stapling technique with previous methods. There are, moreover, several crucial points in the procedure which may facilitate uneventful healing. Thus the gap between the anvil and the staple cartridge must be large enough to accomodate the tissue. On the other hand, the

TABLE IV

TOTAL GASTRECTOMY AND ESOPHAGO-JEJUNOSTOMY WITH DIFFERENT STAPLING DEVICES AND TECHNIQUES. RESULTS* OF FOUR SERIES.

MATERIALS	TECHNIQUE	TYPE OF STAPLER	FAILURE	ANASTOMOTIC LEAKAGE	STRICTURE
Y SANNOHE JAPAN 1981		SPTU	0	2/14	1
H K GRAHAM ⁺ GREAT BRITAIN 1981		SPTU EEA	1	0/13	?
R HUTTUNEN [‡] FINLAND 1982		EEA	0	2/16	1
LUND SWEDEN 1984		EEA	1	3/26	0

* NO DIFFERENCES BETWEEN GROUPS CONCERNING LEAKAGE, FAILURE OR STRICTURE FORMATION, FISHER'S EXACT PROBABILITY TEST.

⁺ X-RAY OF THE ANASTOMOSES ONLY ON CLINICAL SUSPICION OF LEAKAGE.

[‡] USUALLY REINFORCING SUTURES ALSO FASTENING THE ANASTOMOSIS TO THE DIAPHRAGM.

loading unit should be small enough to be inserted into the esophagus. In our experience this is best achieved with the end-to-side approach which permits the jejunal wall to be flattened and thinned, and the 28 mm cartridge which leaves enough space for the more bulky esophageal end. In the present series the 25 mm cartridge was used three times. Two of these anastomoses leaked. The third leakage occurred after an incomplete "doughnut". If one of the "doughnuts" is found to be incomplete the anastomosis must not be accepted until a leak is found and oversewn.

The development of a stricture is a serious complication, since one of the main goals of surgical treatment in these patients is to relieve dysphagia. A stricture is generally the result of a leaking anastomosis but may also evolve irrespective of it. The progressive widening of the anastomosis during the first three months in the present series is probably due to repeated dilatation caused by the passage of food. The staple row of multiple "single stitches" allows elongation of the tissue in between. A manually placed suture line of reinforcing stitches should therefore only be used when a leakage is suspected or verified since the procedure may narrow the lumen and counteract widening of the anastomosis. In their series of 31 EEA esophago-gastrostomies West and others (19) found non-malignant strictures in four patients. The 25 mm cartridge had been used in three of these patients. In spite of a small number of

complications with the 25 mm cartridge 2/3 leakage in the present series, and 3/4 strictures in the series of West and others (19) we recommend the use of the largest loading unit the esophageal lumen can accept.

In one patient the esophagus tore and the anastomosis had to be sutured by hand. Every surgeon using stapling devices must therefore be prepared to hand-suture the anastomosis. The best way to avoid tearing is to divide the esophagus as distal as possible, recognizing the strong circular muscle fibres of the cardia, known to be resistant to dilatation.

Since most of the surgery for gastric carcinoma is palliative (20) the postoperative morbidity and mortality should be low and the postoperative hospital stay short. The ability to swallow should be maintained for the rest of the patient's life. We consider the EEA-stapler to be of great value in fulfilling these demands.

In conclusion, the end-to-side esophagojejunostomy constructed with the EEA-stapler inserted through the open jejunal end allows a fast, reliable anastomosis in the abdomen or in the right or left chest after total gastrectomy for gastric carcinoma.

Since most of the surgery for gastric carcinoma is palliative the postoperative morbidity and mortality should be low and the postoperative hospital stay short. The ability to swallow shall be maintained for the rest of the patient's life. We consider the EEA-stapler to be of great value to fulfilling these demands.

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Effect of Paraesophageal Hernia on Sphincter Function And its Implication on Surgical Therapy

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A paraesophageal hernia differs from a sliding hiatal hernia by posterior fixation of the cardia to the periaortic fascia. This anchors an adequate segment of the lower esophageal sphincter within the abdomen and maintains its competency [1]. This clinical observation has not been confirmed with current physiologic testing and has been challenged by others who have observed an incompetent cardia in patients with a paraesophageal hernia. Because a dispute exists over this issue, a variety of different surgical procedures have been recommended for the repair of a paraesophageal hernia. They vary from simple closure of the hiatus anterior to the esophagus after reduction of the herniated stomach [2] to complete dissection of the esophageal hiatus and reconstruction of the cardia with an antireflux procedure [3]. The former approach is necessary if the cardia in a patient with paraesophageal hernia is competent, whereas a form of antireflux repair is necessary to prevent subsequent reflux symptoms if the cardia is incompetent.

Paraesophageal hiatal hernias can be asymptomatic until a vascular compromise occurs, causing bleeding, infarction, and perforation [4]. The onset of these complications indicates immediate surgical correction. Consequently, the clinical presentation of these patients does not always provide the opportunity for individual preoperative testing. To provide the surgeon with an understanding of the pathophysiologic aspects of paraesophageal hernia and a rationale for an urgent procedure, we studied the cardia in patients with identifiable paraesophageal hernias using esophageal manometry and 24 hour pH monitoring. The findings were compared with those observed in patients with a sliding hernia and in normal control subjects.

Material and Methods

The normal control subjects consisted of 18 patients with no history or symptoms of gastroesophageal reflux, no previous antacid therapy, no previous upper gastrointestinal radiographic study for digestive symptoms, and a normal upper gastrointestinal radiogram at the time of voluntary induction into the study. The study population consisted of 24 patients with suspicion of a paraesophageal hiatal hernia admitted to The University of Chicago between 1976 and 1981. Under strict radiographic criteria as to the location of the gastroesophageal junction, six were thought to have a mixed sliding, paraesophageal hernia. The remaining 18 had a pure paraesophageal hernia with the gastroesophageal junction located well within the abdomen and a portion of the stomach displaced in the chest [5]. Of the 18 patients, 15 had an esophageal motility study and 24 hour esophageal pH monitoring before surgical repair. None of the patients had previous surgery. There were 12 female and 6 male patients. The median age was 68 years, ranging between 36 and 72.

A second study population consisted of 34 patients with sliding hiatal hernias who were randomly selected from those observed during the same period. In each of them, the presence of a hiatal hernia was determined by fiberoptic esophagoscopy, with the patient resting in the left lateral position and breathing quietly, by observing a gastric pouch lined with rugal folds extending at least 2 cm above the crural impression identified by having the patient sniff. No special respiratory maneuvers were employed to increase abdominal pressure and encourage herniation. Each patient identified as having a hernia by endoscopic criteria was confirmed to have a hiatal hernia radiographically.

Each patient was graded on a scale of 0 to 3 for symptoms of heartburn, regurgitation, and dysphagia by means of a reflux questionnaire completed by one of us before the performance of any study (Table I). The highest obtainable score for each symptom was 3 which would represent heartburn that interfered with daily activities, regurgitation associated with episodes of pulmonary aspiration, and dysphagia that required hospital administration for relief of food impaction.

Esophageal manometry was performed according to the technique of Winans and Harris [6] using a single catheter assembly consisting of three fluid-filled polyethylene tubes bonded together with three 2 mm lateral openings placed

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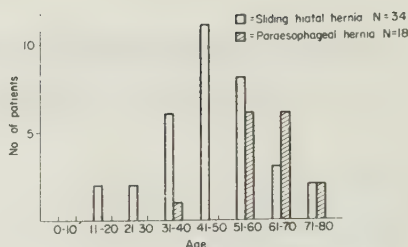
Presented at the 24th Annual Meeting of the Society for Surgery of the Alimentary Tract, Washington, DC, May 24-25, 1983.

TABLE I Symptoms of Gastroesophageal Reflux

Symptom	Grade	Description
Heartburn		
None	0	No heartburn
Minimal	1	Occasional episodes
Moderate	2	Reason for medical visit
Severe	3	Interference with daily activities
Regurgitation		
None	0	No regurgitation
Minimal	1	Occasional episodes
Moderate	2	Predictable on position or straining
Severe	3	Episodes of pulmonary aspiration manifested by chronic nocturnal cough or recurrent pneumonia
Dysphagia		
None	0	No dysphagia
Minimal	1	Occasional episodes
Moderate	2	Required liquids to clear
Severe	3	Episode of food impaction requiring medical treatment

5 cm apart at the assembly's distal end. The catheter was passed into the stomach and withdrawn in 1 cm intervals into the esophagus and up into the pharynx while being perfused with sterile water by means of a pneumohydraulic capillary infusion system at a rate of 0.5 ml/min. By this technique, the location and resting pressure of the lower esophageal sphincter and the location of the respiratory inversion point were obtained. The sphincter pressure was measured in millimeters of mercury as the difference between the resting end expiratory gastric pressure and the distal esophageal sphincter pressure at the respiratory inversion point. The length of lower esophageal sphincter below the respiratory inversion point was determined by measuring the length of the distal esophageal high pressure zone affected by positive excursion associated with respiration.

Twenty-four hour esophageal pH monitoring was performed according to the technique previously described by one of us [7]. A pH electrode was placed 5 cm above the upper border of the lower esophageal sphincter located by manometry, and a reference lead was placed on the non-dominant forearm using a method that assured good electrical contact. Both the pH probe and the reference lead were connected through a pH meter to a strip-chart recorder running at a speed of 6 inches per hour for 24 hours. A normal diet was served during this period unique only in the absence of food and beverages having a pH value of less than 5 or more than 6. All patients were requested to write on the chart recorder their subjective symptoms and body position, that is, whether upright or supine. Acid reflux was detected whenever the pH in the esophagus decreased to less than 4. From the 24 hour record the percent of time the pH was less than 4 in the distal esophagus was determined for the full 24 hours and for the upright and supine periods. In addition, the total number of reflux episodes, the number of episodes greater than 5 minutes, and the length of the longest reflux episode were obtained from the tracing. The normal value for the 24 hour pH test was obtained from the 15 control subjects [7]. The reflux status of individual patients and control subjects was assessed by a 24 hour pH composite score that incorporated the six components of the 24 hour record.

**Figure 1. Comparison of the age incidence of paraesophageal and sliding hiatal hernias according to patient age.**

A normal probability plot was constructed to test whether there was a normal distribution of the data. If so, the Student's *t* test was used for unpaired data. If not, the Mann-Whitney nonparametric test for comparing medians was used. For comparison of percentages, Fisher's exact test was used.

Results

Figure 1 shows the age distributions of patients with a paraesophageal and sliding hiatal hernias. The highest incidence of paraesophageal hernias occurred at a significantly older patient age than that of sliding hernias, median of 61 versus 48 years ($p < 0.001$).

Although several patients with a paraesophageal hernia experienced heartburn and regurgitation, dysphagia was the main complaint. Heartburn was the more common complaint in patients with a sliding hernia. Patients with a paraesophageal hernia also complained of postprandial fullness, epigastric pain, and episodes of hematemesis. The latter occurred in 5 of the 18 patients, and in 4 of the 5 it occurred three times. On the contrary, these symptoms were not observed in patients with a sliding hernia.

All patients had esophagogastrosocopy. Seventeen of the 34 patients with a sliding hernia had endoscopic evidence of esophagitis, 9 with grade I and 8 with grade II. Two of 15 patients with a paraesophageal hernia had grade I esophagitis. Three additional patients had a gastric ulcer at the point of diaphragmatic indentation of the herniated stomach. The distal stomach could be entered in all patients with a sliding hernia but only in 5 of the 15 patients with a paraesophageal hernia.

Figures 2 and 3 show the results of 24 hour esophageal pH monitoring. Sixty percent of patients with a paraesophageal hernia had abnormal acid exposure of the esophagus and an incompetent cardia. There was no relation between the symptoms experienced by the patient and the competency of the cardia (Table II). With the exception of heartburn, this was also true for patients with a sliding hernia.

There was no statistical difference in lower esophageal sphincter pressure between the control

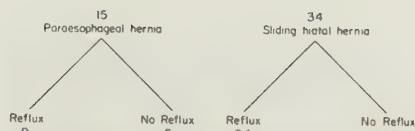


Figure 2. Results of 24 hour pH monitoring in patients with paraesophageal and sliding hiatal hernias. Pathologic reflux was determined by an abnormal 24 hour pH score.

subjects, the patients with paraesophageal hernia with a competent or incompetent cardia, or the patients with a sliding hernia with a competent cardia. However, patients with a sliding hernia and an incompetent cardia had a statistically lower lower esophageal sphincter pressure. The abdominal segment of the lower esophageal sphincter was statistically shorter in patients with an incompetent cardia, particularly in those who had a paraesophageal hernia, and their sphincters were also statistically shorter in their overall length (Figure 4). When integrated, these findings showed that patients with a sliding hernia and an incompetent cardia have a lower esophageal sphincter of normal length but poor tone and an inadequate segment exposed to abdominal pressure. In contrast, patients with a paraesophageal hernia and an incompetent cardia had a very short lower esophageal sphincter with normal tone but with virtually none of it exposed to abdominal pressure. Patients with incompetent cardias and either a paraesophageal or sliding hernia had a similar delayed clearance of acid from their esophagus as reflected in the number of reflux episodes that lasted 5 minutes or longer (Figure 5). No effort was made

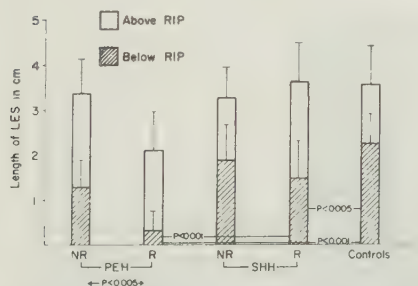


Figure 4. Comparison of the overall length of the lower esophageal sphincter (LES) and the length of the abdominal segment in patients with a paraesophageal or sliding hiatal hernia (PEH and SHH, respectively) and a competent or incompetent cardia to the normal control subjects. NR = no reflux; R = reflux; RIP = respiratory inversion point.

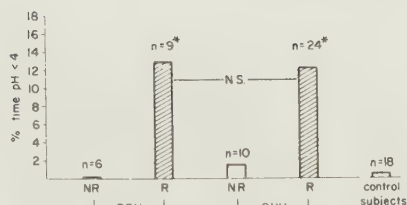


Figure 3. Percent of time intraesophageal pH is below 4 in patients with paraesophageal or sliding hiatal hernia (PEH and SHH, respectively) with a competent or incompetent cardia compared with normal control subjects based on the 24 hour pH score. Asterisks indicate statistical significance between the patients with reflux (R) in the PEH ($p < 0.002$) and SHH ($p < 0.001$) groups versus the corresponding patients without reflux (NR) and the control subjects. NS = not significant.

TABLE II Symptoms of Paraesophageal Hernia Compared With Results of 24 Hour Esophageal pH Monitoring*

Status	Positive	Negative
Heartburn	6 of 9	4 of 6
Regurgitation	6 of 9	3 of 6
Dysphagia	6 of 9	4 of 6
Postprandial fullness	8 of 9	3 of 6
Bleeding	4 of 9	1 of 6

* There was no statistical differences between the groups by Fisher's exact test.

to determine if the delay in acid clearance was due to an excessive volume of refluxed material, repetitive unrecognized reflux episodes, or esophageal dysmotility.

All 15 patients studied had surgical repair of the

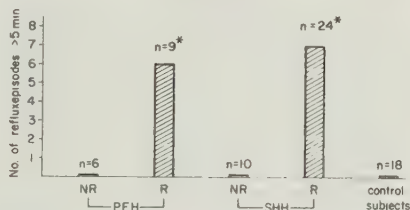


Figure 5. Comparison of acid clearance from the esophagus determined by the number of reflux episodes of 5 minute or longer duration in patients with paraesophageal or sliding hiatal hernia (PEH and SHH, respectively) and competent or incompetent cardia with normal control subjects. Asterisks indicate statistical significance between the patients with reflux (R) in the PEH ($p < 0.002$) and SHH ($p < 0.001$) groups versus the corresponding patients without reflux (NR) and the control subjects.

TABLE III Surgical Follow-Up Data

Patient	Sphincter Length (cm)		Abdominal Length (cm)	
	Preoperatively	Postoperatively	Preoperatively	Postoperatively
1	3.7	4.6	1.1	2.3
2	1.5	3	0.5	3
3	4	5	0.5	3.5

paraesophageal hernia. Nine had a transthoracic Nissen fundoplication, one an abdominal Nissen fundoplication, and five a Belsey Mark IV procedure. Eight patients were followed for a mean of 3 years (range 2 to 7 years). Of the remaining seven patients, two died and five could not be contacted. All patients reported relief of preoperative symptoms. Three patients volunteered for postoperative motility studies and a standard acid reflux test. All were free of reflux and on motility had an increase in both the overall sphincter length and the segment exposed to abdominal pressure (Table III).

Comments

There is general agreement that a paraesophageal hernia should be operated on shortly after diagnosis to avoid the life-threatening complications of bleeding, infarction, and perforation [8-11]. The importance of this opinion is supported by the observation that a third of our patients experienced hematemesis and several had more than one episode.

Physiologic studies showed that 60 percent of patients with a paraesophageal hernia had an incompetent cardia which was associated with a shortening of the lower esophageal sphincter length and its displacement outside the environment of the abdomen. This does not occur with a sliding hernia, even

though it appears to be within the chest on a roentgenographic barium study, because a sliding hernia has a sac that functions as an extension of the abdominal cavity, whereas a paraesophageal hernia occurs partially by way of an extraperitoneal route through a widened hiatus to reach the chest, and a portion of the stomach and cardia can form part of the wall of the hernia sack. Consequently, the lower esophageal sphincter, if displaced, lies outside the abdominal cavity and is unaffected by its environmental pressures. In essence, a paraesophageal hiatal hernia is similar in development to a sliding inguinal hernia.

With time, some patients with a pure paraesophageal hernia lose fixation of the lower esophageal sphincter, and an associated sliding hernia develops. This explains why a mixed type of hernia was seen in 6 of the initial 24 patients evaluated. The possibility of this event supports the wisdom of performing an antireflux procedure with each repair (Figure 6).

As a consequence to these pathophysiologic findings and the results of our surgical experience, we recommend that repair of a paraesophageal hernia include an antireflux procedure to correct the sphincter characteristics associated with a mechanically incompetent cardia. This is particularly so when the operation is performed on an urgent basis without preoperative studies. If time permits, pre-

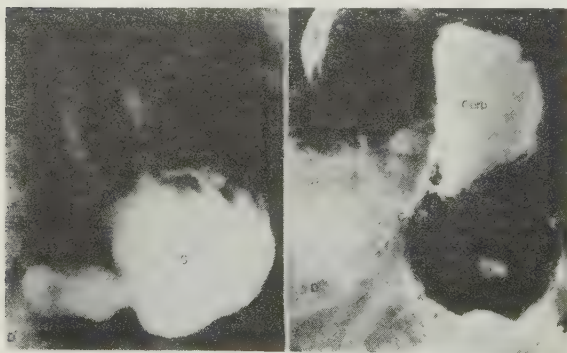


Figure 6. Left, upper gastrointestinal barium contrast study showing a pure paraesophageal hernia in a patient in whom a mixed paraesophageal and sliding hiatal hernia subsequently developed. Right, a similar roentgenogram taken 6 years later. C = cardia; Corp = body of stomach; D = duodenum; E = esophagus; F = fundus of stomach; H = paraesophageal hernia; S = stomach.

operative evaluation with 24 hour esophageal pH monitoring and esophageal manometry allows the identification of patients with competent cardias. Such patients might be candidates for the anatomic repair proposed by Hill and Tobias [2,12] if the surgical dissection itself does not alter the function of the cardia.

Summary

Fifteen patients with a paraesophageal hernia were studied with 24 hour esophageal pH monitoring and esophageal manometry to clarify the physiologic aspects of the cardia and resolve controversies over the type of surgical repair. The results were compared with those obtained in 34 randomly selected patients with a sliding hernia and 18 normal control subjects. Sixty percent of the patients with a paraesophageal hernia had an incompetent cardia on 24 hour pH studies which was associated with a lower esophageal sphincter of normal pressure, short overall length, and a small segment exposed to abdominal pressure. In comparison, 70 percent of patients with a sliding hernia had an incompetent cardia which was associated with a lower esophageal sphincter of low pressure, normal overall length, and a short segment exposed to abdominal pressure. With either type of hernia, symptoms were not helpful in determining the competency of the cardia. When urgent surgery is necessary, repair should include an antireflux procedure. If facilities and time permit, more specific evaluation of the cardia can be performed, and if competent, the repair should be limited to reduction of the stomach and closure of the defect.

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Discussion

Philip E. Donahue (Chicago, IL): This excellent presentation from the University of Chicago is of great interest because its conclusions challenge traditional concepts relating to paraesophageal hiatal hernia, including the idea that it is rarely associated with reflux. My question relates to the concept of lower esophageal sphincter function proposed by Petterson and Bombeck in Illinois. They proposed that reflux episodes are initiated by stretching of the lower esophagus sphincter which accompanies distention of the stomach. Furthermore, in an experimental model, if distention of the stomach is prevented either by Nissen fundoplication, simple silk suture, or experimental hiatal hernia, the tendency to reflux diminishes. So, by their postulate a hiatal hernia, sliding or paraesophageal, reduces the tendency to reflux. However, in the patients in the present study, several were shown to have reflux regardless of the nature of their presenting symptoms. We suggest that their nonspecific foregut symptoms could all be explained by incarceration of that paraesophageal hernia. When such patients have reflux, they do so because of increased intragastric pressure in that incarcerated segment, so they do not really have primary reflux but a secondary type of gastroesophageal reflux similar to that seen in gastric outlet obstruction.

I would like to ask the authors to reconcile this concept with their presentation and also to explain why patients operated on for paraesophageal hernia by hernia reduction alone do not have pathologic reflux, as your presentation implies.

George F. Gowen (Pottstown, PA): I agree that the symptoms are more related to obstruction with dysphagia than with heartburn. In a series of six patients, we found outflow obstruction when more than half the stomach was above the diaphragm. The upper gastrointestinal series is not very helpful except to show the retained barium in a stomach above the diaphragm, and it is equally ineffective in evaluating the mucosal surface of the herniated stomach. One of my patients had an unsuspected carcinoma of the stomach undetected by the upper gastrointestinal series and endoscopy.

Whereas a sliding hiatal hernia is frequently associated with esophagitis, the paraesophageal hernia is a disease in itself waiting for an obstruction to occur. When the stomach goes up, so does the spleen. The end stage of the disease is an upside down stomach. We need to perform hiatal herniorrhaphy with Nissen fundoplication at an earlier stage. Dr. DeMeester, how do you close the hiatus that is usually 12 to 15 cm in diameter? Do you push the esophagus posteriorly against the aorta or bring it anteriorly into the dome?

Arthur Sicular (New York, NY): I enjoyed the data and the method of approach in studying these patients. My personal observations indicate that simple reduction of paraesophageal hernia certainly may restore many of these competency mechanisms without adding a Nissen plication. I wonder, in a study of elective repair of paraesophageal hernia, how many symptoms may be due to reflux. In patients in whom I have added a sphincter-supporting procedure, there is a preoperative history of reflux. However, a few patients in whom I simply repaired the hernia

with standard methods of reduction and diaphragm closure have had dysphagia postoperatively.

W. Silber (Cape Town, South Africa): The authors illustrated a paraesophageal hernia coming through the opening. An esophageal hernia coming through the esophageal hiatus is rare and is usually associated with a sliding hiatal hernia. In fact, it is usually a mixed hernia. The true paraesophageal hernia comes through a congenital opening in the diaphragm. In our series of 51 cases of true paraesophageal hernia, dysphagia was usually due to pressure of the paraesophageal hernia on the lower end of the esophagus. Only 2 of 51 patients had reflux and heartburn. Dr. DeMeester, do you agree that the dysphagia is due to pressure of the paraesophageal component?

Dr. Cohen (New York, NY): I compliment the authors on a sorely needed paper in this area. Sometimes there can be a correlation between the length of the intraabdominal segment and the width of the hiatus on radiologic examination. A patulous or widened hiatal orifice may be one reflection of lax ligaments and can be associated with a short intraabdominal segment. Many of these patients can be managed by medical therapy and do not have episodes of incarceration of the paraesophageal component. Dr. DeMeester, have you noted any correlation with the radiologic observation of a patulous hiatal orifice?

K. Johansson (Stockholm, Sweden): Were these hernias real paraesophageal hernias? Perhaps they were a mixture of sliding hiatal hernia and paraesophageal hernia.

Tom R. DeMeester (closing): We did not include in our study the mixed type of hernia, that is, both a sliding and a paraesophageal hernia. We initially had 24 patients, but 6 were excluded when we were unsure radiographically if the distal esophageal sphincter was within the abdomen. We were surprised that 60 percent of these selected patients had reflux on 24 hour esophageal pH monitoring and also had symptoms of heartburn and regurgitation. The only symptom that differentiated the paraesophageal from the sliding hernia was the higher incidence of dysphagia, hemoptysis, and ulceration.

Closure of the hiatus can be a problem with paraesophageal hernia, and recurrence is often due to its breakdown. The use of Teflon® pledgets to strengthen the closure is helpful. We have not used a wide hiatus as an indication for surgical as opposed to medical treatment. Neither could this decision be based on whether the cardia was competent or not, because it was not related to the development of symptoms associated with intrathoracic dilatation of the stomach. The presence of a paraesophageal hernia was the only indication for its repair.

When performing an urgent operation, we recommend that an antireflux procedure be performed with repair of the hernia because the surgeon is unaware of the amount of reflux present and it would remain uncorrected. However, if the presence of a competent sphincter can be determined preoperatively by a 24 hour esophageal pH monitoring study, and if the dissection does not disrupt the antireflux mechanism, then simple closure of the hiatus may be the thing to do and will be most beneficial to the patient.

GASTRIC DILATATION, INTRAGASTRIC PRESSURE AND
ESOPHAGEAL TENSION AS DETERMINANTS OF CARDIAC COMPETENCY

by

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ABSTRACT

Clinical and experimental findings have shown that gastro-esophageal reflux results when cardia is incompetent. In a unique in vitro model the influence of overall sphincter length, esophageal tension and gastroesophageal outlet diameter, i.e. gastric distension, was studied on the ability of the cardia to remain competent. In a separate experiment utilizing the same model the quotient between sphincter pressure and intragastric pressure was related to the overall sphincter length necessary to maintain complete competency. A total of 83 freshly harvested dog specimens were examined. When physiologic tension was applied complete competency was obtained when the overall sphincter length was 3.0 cm or more and the gastric outlet diameter was 60 Fr or less. Increasing the size of the gastric outlet and/or tension consistently resulted in decreased competency, which could be compensated for by increased sphincter length. In the extreme situation of maximal tension and gastric outlet diameter competency was almost totally abolished despite overall maximal sphincter length (5 cm). When the quotient of sphincter pressure over intragastric pressure exceeded one the degree of competency depended upon the overall sphincter length present whereas a quotient less than one consistently resulted in decreased competency even with a maximal sphincter length. These findings not only contribute to the understanding of the pathophysiology of gastroesophageal reflux but also adds valuable information as to what principles should be attempted in the surgical treatment of this disorder.

INTRODUCTION

Previous clinical studies have shown that the intraabdominal length and the resting pressure of the lower esophageal sphincter are important factors in maintaining cardiac competency (1 - 3). The importance of these findings was further supported by the results of experimental studies in a model permitting a standardized variation not only of sphincter length and pressure but also of intragastric, intraabdominal and intrathoracic pressures (1). Thus, the concept that cardia with its sphincter zone exerts its antireflux capacity rather on mechanical than physiologic and pharmacologic grounds was emphasized. As, however, reflux can occur in patients with normal sphincter pressure and abdominal sphincter length other mechanisms influencing cardiac competency must be involved. The observation that patients with delayed gastric emptying seem to be more exposed to reflux has focused attention to the role of intragastric pressure and gastric dilatation in the pathophysiology of gastroesophageal reflux (4).

In the present study the influence of the overall sphincter length, the axial tension of the distal esophagus and the gastric dilatation or outlet diameter on the ability of the cardia to remain competent against challenges of an intragastric pressure independent of intraabdominal and sphincter pressure, was evaluated. In a separate experiment the overall sphincter length was related to the relationship between sphincter pressure and intragastric pressure when complete competency was maintained.

METHODS

Gastroesophageal specimens were removed from anesthetized dogs, which had previously not undergone any procedures related to the area. Before the removal two stitches were placed in the esophagus, one stitch on the phrenicoesophageal ligament where it attached to the esophageal wall and the other five cm above in the esophageal wall. These stitches were used to facilitate determination of the in vivo length and physiologic tension when the specimen was placed in the in vitro model. All specimens were preserved in saline solution at 4 C for no more than four hours before examination in the model. A total of 83 specimens were used.

The model used in this study (Figure 1) represents a modification and further development of our previously used model (1). A constant pressure gastric reservoir, marked A, which could be adjusted for various levels of gastric pressure, functioned as the gastric challenge for reflux to occur. The gastroesophageal specimen was placed within an abdominal chamber connected to a second reservoir, marked B, which could be adjusted to set various levels of pressure. This pressure represents the summation of the intraabdominal and the sphincter pressures and is measured utilizing the manometer number 2. Under normal physiologic circumstances, intragastric pressure is essentially equal to intraabdominal pressure; therefore, any increase of intraabdominal pressure in excess of intragastric pressure can,

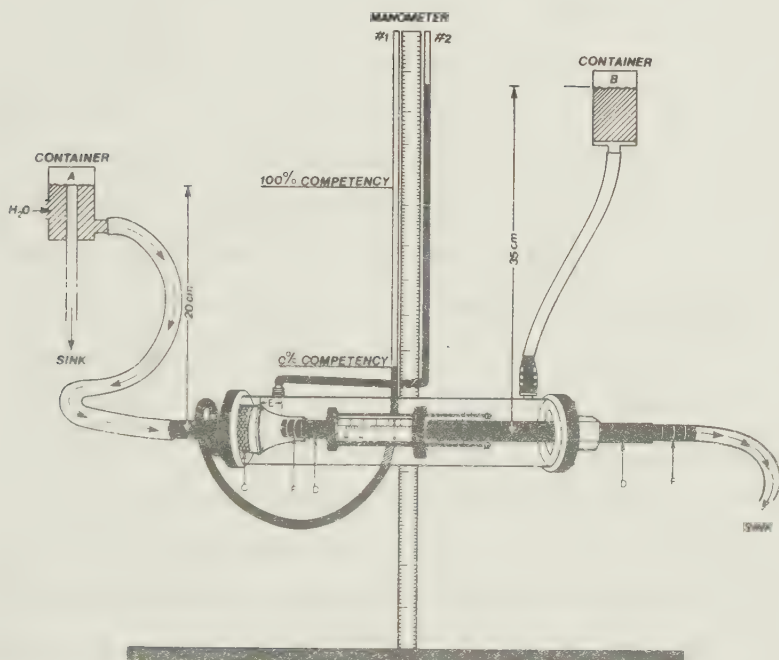


Figure 1. Schematic drawing of the model used to study the factors involved in the determination of cardiac competency. For details see Methods.

for all technical purposes, be considered tone within the esophageal muscle, even though it was artificially produced. The distal or gastric end of the specimen was attached to an interchangeable part (marked C) of the abdominal chamber. The interchangeable parts differed from each other by varying outlet diameter of the tube that passed through it. After placement of

the specimen under physiologic tension, the latter could be increased by continuous stretching of the specimen. This was achieved by sliding the tube (marked D) connected to the proximal end of the specimen in the direction out of the abdominal chamber. This movement was opposed by three metal springs within the chamber. A scale with markings for tensions corresponding to one and two kilodyne was used for adjustment of the desired tension. The length of the esophagus exposed to the abdominal pressure, marked E, was adjusted by placing a stent (marked F) through the esophagus, allowing only the unstented portion of it to be acted upon by the chamber pressure. Competency was determined by measuring the resistance to flow from the gastric reservoir through the specimen. This was done using the manometer number 1. Zero competency was defined as the fluid level in manometer number 1 when the whole esophagus was stented open and, therefore, no portion of it was exposed to the chamber pressure. One hundred percent competency was defined as the cessation of all flow and was indicated by a rise in the fluid level of manometer number 1 equal to the level of the gastric reservoir. Partial competency was calculated as the percentage of the rise in the fluid level in manometer number 1 between these two levels.

It is thus possible to vary all of the following parameters: overall sphincter length, sphincter pressure, intragastric pressure, intraabdominal pressure, esophageal tension and

gastric outlet diameter. If desired the effect of intrathoracic pressure can be analyzed by attachment of a siphon, through which the outflow from the gastroesophageal tube can pass. This opportunity was not used in this study.

In Experiment I the intragastric, intraabdominal and sphincter pressures were kept constant during the experiments (Table I). The sphincter length exposed to the chamber pressure varied from zero to five centimeters. Three different degrees of esophageal tension was applied and four different sizes of gastroesophageal outlet diameter (Tables II and III). Every specimen was used only once and in a given combination of esophageal tension and gastric outlet diameter. Consequently 12 groups were evaluated and in each group the sphincter length was increased by increments of 0.5 cm from zero to five centimeters with measurement of the competency after an equilibration period of 30-45 seconds per increment. The number of specimens used per group varied from three to six.

Table I

THREE FACTORS KEPT CONSTANT IN EXPERIMENT I

Intragastric pressure	20 cm H ₂ O
Intraabdominal pressure	20 cm H ₂ O
Sphincter pressure	15 cm H ₂ O

Table II

ESOPHAGEAL TENSION USED IN EXPERIMENT I

Physiologic tension

- 1 KiloDyne
- 2 KiloDyne

Table III

GASTRIC OUTLET DIAMETERS USED IN EXPERIMENT I

1.0 cm	Approximates	30 Fr
1.5 cm	"	45 Fr
2.0 cm	"	60 Fr
3.0 cm	"	90 Fr

In Experiment II including 20 specimens the intragastric and intraabdominal pressures were kept constant at 20 cm H₂O, whereas sphincter pressure was varied between zero and 100 cm H₂O. As sphincter pressure was gradually increased the overall length of the sphincter necessary to achieve complete competency was determined.

RESULTS

Relationship between Esophageal Tension and Competency of the Cardia

(Experiment I)

Increased esophageal tension consistently resulted in decreased competency when the gastric outlet diameter and sphincter length were constant. Figure 2 illustrates this relationship for a gastric outlet diameter of 1.0 cm and a sphincter length of 3.0 cm. The effects of increased tension on sphincter competency was possible to reverse by increasing the sphincter length. When, however, maximal tension was applied complete competency was not restored even with maximal (5 cm) sphincter length (Fig 3). The relationship between esophageal tension and sphincter length is illustrated in Figure 4 for two different situations; complete and incomplete (50%) competency. Again the importance of sufficient length in the prevention of reflux is underlined.

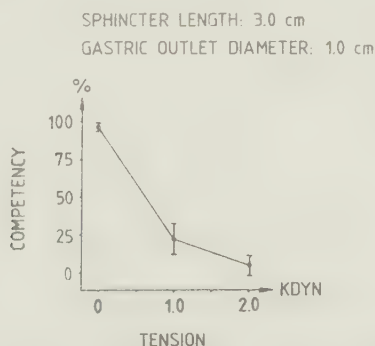


Figure 2. Relationship between esophageal tension and competency of cardia. Sphincter length (3 cm) and gastric outlet diameter (1.0 cm) were kept constant. Mean $\pm$ SEM.

GASTRIC OUTLET DIAMETER: 1.0 cm

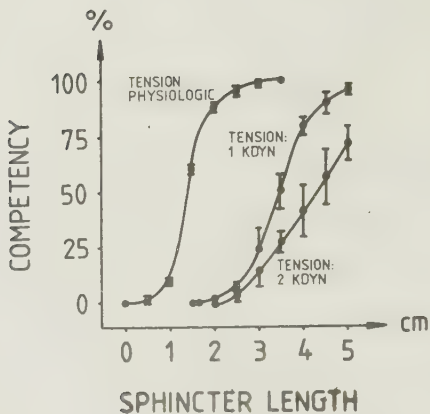


Figure 3. Effect of overall sphincter length on the competency of cardia when three different tensions were applied. Gastric outlet diameter (1.0 cm) was kept constant. Mean $\pm$ SEM.

GASTRIC OUTLET DIAMETER: 1.0 cm

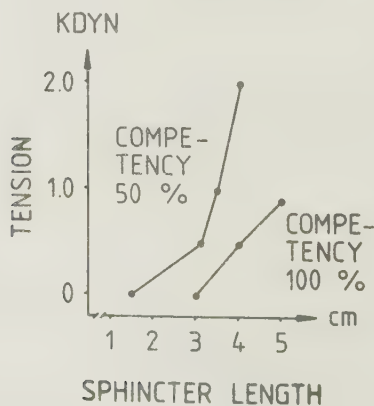


Figure 4. Relationship between overall sphincter length and esophageal tension, when complete and incomplete competency was attempted. Gastric outlet diameter (1.0 cm) was kept constant.

Relationship between the Sphincter and Intragastric Pressures and Competency of the Cardia

(Experiment II)

In this experiment sphincter pressure was gradually increased whereas intragastric pressure was unchanged. The ratio of sphincter over intragastric pressure was therefore changed from an initial value of one up to five. Figure 5 illustrates how the increased ratio reduces the necessary sphincter length to achieve complete competency. The slope of the curve infinitely approaches a sphincter length of zero as further increase of the ratio takes place. On the other hand is the observation that a sphincter, exceeding 5.0 cm of length is unable to maintain complete competency when intragastric pressure is greater than sphincter pressure, i.e. when the ratio is less than one.

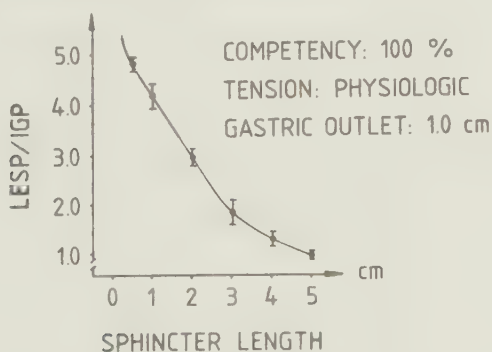


Figure 5. Interrelationship between overall sphincter length and the quotient of sphincter pressure (LESP) and intragastric pressure (IGP) when complete competency was present. Gastric outlet diameter (1.0 cm) and esophageal tension (physiologic) was kept constant. Mean $\pm$ SEM.

Relationship between Gastric Dilatation and
Competency of the Cardia

(Experiment I)

In Figure 6 is shown how the diameter of the gastroesophageal outlet in a significant way influenced the resistance to flow through the specimen. Maximal outlet diameter (3.0 cm) with constant esophageal tension and sphincter length increased the gastroesophageal flow more than fourfold when compared to a gastric outlet of 1.0 cm. Thus increased diameter decreased competency. With a gastroesophageal outlet of 1.0 cm complete competency was achieved when esophageal tension was physiologic and sphincter length exceeded 3.0 cm (Fig. 7). The effects of increased gastric outlet diameter were reversed by increasing the sphincter length. It was, however, not possible to completely restore full competency even with maximal (i.e., 5 cm) length (Fig. 7). In Figure 8 the relationship between gastric outlet diameter and sphincter length is presented when complete or incomplete (50%) competency was at hand. An overall sphincter length of less than 3 cm is likely to result in some degree of reflux.

SPHINCTER LENGTH: 2.0 cm

TENSION: PHYSIOLOGIC

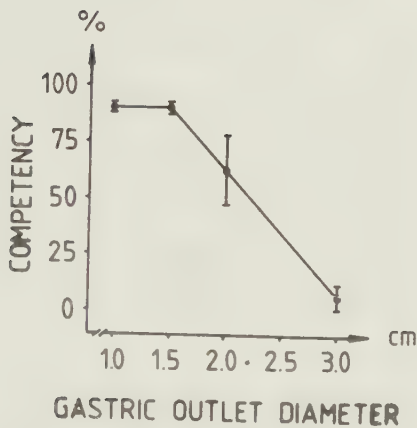


Figure 6. Relationship between gastric outlet diameter and competency of cardia when overall sphincter length (2.0 cm) and tension (physiologic) was kept constant. Mean $\pm$ SEM.

TENSION: PHYSIOLOGIC

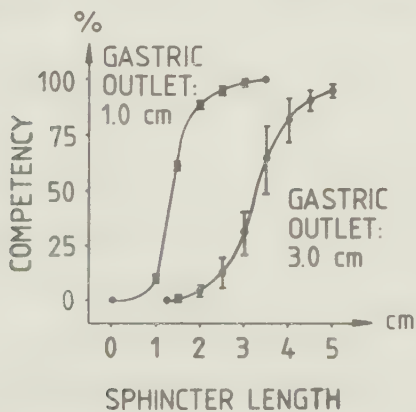


Figure 7. Effect of the overall sphincter length on competency of cardia when gastric outlet diameter was 1.0 cm and 3.0 cm respectively. Physiologic tension was applied and kept konstant. Mean $\pm$ SEM.

TENSION: PHYSIOLOGIC

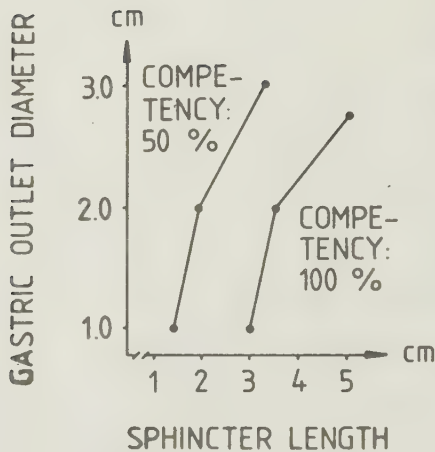


Figure 8. Interrelationship between overall sphincter length and gastric outlet diameter for complete (100%) and incomplete (50%) competency of cardia when physiologic tension was applied.

Influence of Sphincter Length on Cardiac Competency

(Experiments I and II)

In both experiments it was nicely shown how the overall sphincter length influenced competency. Under conditions corresponding to a basal, physiologic situation, i.e. "in vivo" tension, a gastric outlet diameter of 1.0 cm and a ratio of sphincter pressure over intragastric pressure exceeding 1.0 the minimal length of the sphincter necessary to maintain complete competency is 3.0 cm. Decreased length consistently resulted in reduced competency unless counteracted by changes of one or several of the other factors involved (Fig. 2-8).

DISCUSSION

The results of the present study clearly demonstrate that the overall sphincter length and pressure, the degree of gastric dilatation, i.e. gastric outlet diameter, the intragastric pressure and the axial tension of the esophagus are important factors in determination of cardiac competency. The results also show that competency is a result of interaction between these factors and that abnormalities of one factor may be neutralized by one or several of the others.

It has long been recognized that sufficient intraabdominal length and pressure of the lower esophageal sphincter are necessary to maintain competency of cardia (5-8). Experimental support for these clinical observations was obtained from studies in an in vitro model that was used in our laboratory prior to the present model (1). It was concluded that competency of a segment of the intraabdominal esophagus without intrinsic tone was directly related to its length and, further, that competency was augmented by the presence of intrinsic tone and that the shorter the length the greater the intrinsic tone needed. Nevertheless alternative pathways promoting reflux have been suggested. Dodds et al (9) investigated normal subjects utilizing a sleeve catheter and were able to show that reflux occurred during brief episodes of complete relaxation of the lower esophageal sphincter. Their findings imply that not only the intraabdominal part but the overall length of the sphincter is important. Our findings in the

present study in fact refer to the overall sphincter length and clearly emphasize the importance of appropriate overall length in maintenance of cardia competency.

In their elegant experiments Pettersson et al (10) suggested that length of the sphincter contributes to competency by decreasing the effects of gastric wall tension. At the same time they introduced the degree of gastric distension as a significant factor in sphincter function. This concept is further elucidated in the present study in which gastric distension was reflected by different outlet diameters as intragastric pressure remained intact. Both studies univocally demonstrate that increasing diameter of the gastroesophageal junction impairs cardiac function if not counteracted by increased length and/or tension.

Little et al (4) demonstrated that delayed gastric emptying was a more frequent finding in patients with gastroesophageal reflux than in controls. The mechanisms involved were not analyzed in detail but it is reasonable to suggest that either dilatation of the stomach, increased intragastric pressure or both were involved. It is, however, inaccurate to assume that gastric dilatation reflects intragastric pressure. In Experiment II of the present study the relationship between intragastric pressure, sphincter pressure and competency therefore was evaluated. Gastric outlet was kept constant. The results showed that decreased ratio of sphincter over intragastric pressures, i.e.

increasing intragastric pressure, decreased competency. When intragastric pressure exceeded sphincter pressure free reflux occurred. As gastric emptying is significantly more rapid in obese subjects than in non obese controls (11) it still remains to be clarified by which pathways gastroesophageal reflux is promoted in these patients as reflux occurs more frequently in obese than non-obese people.

What is the role of hiatal hernia in the pathogenesis of reflux? Although it was shown by DeMeester et al (12) that decreased resting pressure and short intraabdominal length on a population basis were more frequent findings in patients with hiatal hernias and reflux than in patients with hiatal hernias and no reflux there is a wide overlap inbetween individuals from each group. It is also know that reflux occurs more frequently in patients with hiatal hernias than without when their spincter qualities are equal (13). In vivo and in vitro experiments by Pettersson et al (14) demonstrated how the size of the hernia, by influencing gastric wall tension, determined cardiac competency. The larger the hernia the greater the wall tension and the degree of incompetency. Again these findings are in agreement with the findings of the present study, which also shows the deleterious influence of increased gastric outlet cardiac competency.

The main objective of surgery in the treatment of reflux is to reconstruct the normal intraabdominal segment of the esophagus, thereby subjecting it to intraabdominal pressures. Failure to control reflux in spite of this may be explained by the present findings. Unless a meticulous dissection allows intraabdominal replacement without tension, the advantage of increased abdominal length may be completely abolished. Disregard of factors such as delayed gastric emptying will threaten the results of a technically perfect antireflux procedure. On the other hand there seems to be certain optimal limits for e.g. the intraabdominal length which is necessary to obtain complete competency. Our study implies that more than five centimeters length is unnecessary and that three centimeters probably is sufficient. If this is not possible to achieve, a wrap that limits the gastric outlet diameter to less than two centimeters (60 Fr) may be the key to prevention of reflux. From a theoretical standpoint the goals of antireflux procedures that have been outlined above could be achieved by a collar at the gastroesophageal junction in a way that has been attempted by the prosthesis described by Angelchik (15). Three subsequent studies have suggested somewhat different modes of its action. Samelson et al (16) concluded that the silicone antireflux prosthesis acts by interrupting distraction of the lower esophageal sphincter by gastric wall tension whereas Benjamin et al (17) suggest that the effect is due to posterior padding of the esophagogastric junction. Cohen et al (18), finally support the view that the mechanism of action

is due to an increase in length of the lower esophageal sphincter resulting in an increased sphincter pressure when measured before and after insertion of the prosthesis.

In conclusion the results from the present study has confirmed our previous findings that sphincter pressure and sphincter length are important factors in cardiac competency. It has also emphasized the importance of esophageal tension and gastric outlet diameter in this respect. These findings add to the understanding of the complex pathophysiology of gastroesophageal reflux and to the principles of antireflux procedures.

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INFLUENCE OF MORPHINE ON THE DISTAL OESOPHAGUS AND
THE LOWER OESOPHAGEAL SPINCTER - A MANOMETRIC STUDY

Running Title: Morphine effects on oesophageal motility

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ABSTRACT

Basal pressure and relaxation of the lower oesophageal sphincter (LES) as well as amplitude, duration and propagation velocity of peristaltic waves in the distal third of oesophagus were measured in fifteen healthy adults (9♂ and 6 ♀). A highly standardized technique was used employing manometric equipment including a low-compliance pneumohydraulic infusion system and a triple lumen recording catheter. After establishment of baseline manometry values the catheter was positioned with its distal orifice in the LES. In ten subjects 0.2 mg/kg body weight of morphine sulphate was then injected subcutaneously. In five others equal volume of saline was given. The manometric data were analyzed blindly. Repeated manometric evaluations were performed 15, 30, 45, 60 and 75 minutes after the injection. Morphine increased slightly LES-pressure and significantly ($p < 0.001$) decreased LES-relaxation, the maximal effect occurring 30 minutes after the injection. Amplitude of peristaltic waves increased slightly but insignificantly, whereas propagation velocity and duration were uninfluenced. The results of this study suggest that pharmacologic doses of morphine influence normal function of the LES and possibly the distal oesophagus. The role of endogenous opiates in this respect however awaits further studies. It is suggested that abnormalities in opioid neurotransmission may explain some of the non-specific oesophageal motility disorders.

Key Words: Oesophagus, manometry, morphine, motility disorders

INTRODUCTION

It has recently been shown that the oesophageal smooth muscles in addition to adrenergic and cholinergic nerves contain enkephalin immunoreactive nerves (1). Evidence has also been presented suggesting the existence of enkephalin (opiate) receptors in the lower oesophageal sphincter of the opossum (2, 3). As endogenous opioid-like peptides (endorphins) have been identified in the central and enteric nervous system (4, 5) the physiological significance of these findings remains to be clarified. Stacher et al (6) studied the influence of a synthetic met-enkephalin analogue, FK 33-824 on oesophageal motor activity in healthy humans. Their results support a role for enkephalins in the regulation of the oesophageal wave amplitude, duration and propagation velocity. The lower oesophageal sphincter was, however, not studied. The aim of the present study was to investigate the effects of therapeutic doses of morphine on distal esophageal motility and lower oesophageal sphincter function in man.

METHODS

Subjects

Fifteen healthy volunteers, 9 men and 6 women, aged 20 - 27 years (median 23 years) were investigated. None of them had a history of drug abuse or gastroesophageal disease. Informed written consent was obtained and the study was approved by the clinical investigation committee.

Manometric technique

A fluid filled recording catheter (ES 3, oesophageal manometer catheter, Arndorfer Medical Specialties, Greendale, Wisconsin, USA) consisting of three polyethylene tubes was used. Each tube had a 2 mm wide lateral opening near its distal end. The openings were placed 5 cm apart and at 120° angles (Figure 1). The tubes were continuously perfused by a low-compliance, pneumohydraulic capillary infusion pump (Arndorfer Medical Specialties, Greendale, Wisconsin, USA) at a rate of 0.6 ml/minute. Each tube was connected to a transducer (Statham P2306, Gould, Inc., Cleveland, Ohio, USA) and in turn to a direct inkwriting recorder (Hewlett-Packard, 7774B). After topical anesthesia of the nasal passage with 4% Cocaine, the catheter was passed into the stomach of the fasting subject. The catheter was then withdrawn by 1 cm increments into the oesophagus while recordings were made. Location and length of the lower oesophageal sphincter (LES) ^{*} was measured and the position of the point of respiratory inversion (RIP) was noted. With the distal orifice just above RIP, the catheter unit was secured by taping to the nose. The lower oesophageal sphincter pressure (LESP) was calculated at the RIP as the difference between basal expiratory gastric and LES deviations. Relaxation of LES was calculated as the deflection from the basal LES pressure as indicated above expressed in mm Hg

*

The authors are aware that the term lower oesophageal high pressure zone (LEHPZ) is more accurate and further that LES is not equivalent to LEHPZ. From a practical point of view we, however, prefer the term LES.

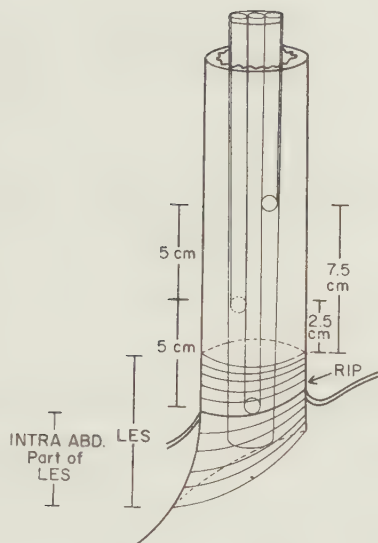


Figure 1. The position of the recording catheter inside the distal part of the oesophagus. LES - Lower esophageal sphincter. RIP - respiratory inversion point.

and as percentage of LESP (Figure 2). Oesophageal body contractions were recorded 5.0 cm and 10.0 cm above RIP (approximately 2.5 cm and 7.5 cm above the LES) (Figure 1).

Amplitude of contractions (mm Hg) was measured from the oesophageal baseline to the peak of the complex. Duration of a contraction (seconds) was measured as the interval from the upstroke of the complex to its return to the baseline. Propagation velocity (cm/s) between the tube openings located 10.0 and 5.0 cm above RIP was calculated after measuring the time interval between the peaks of corresponding complexes. (Figure 2).

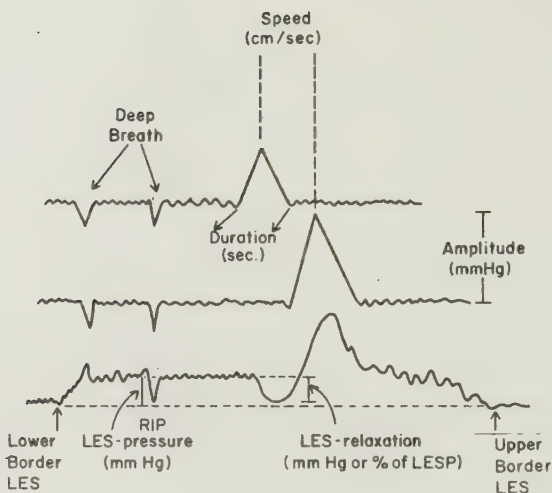


Figure 2. Schematic diagram of reference points used in the manometric evaluations. LES - lower esophageal sphincter. RIP - respiratory inversion point.

Experimental design

The recording catheter was passed trans-nasally into the oesophagus of a fasting subject and fixed as explained above throughout the study. With the subject relaxed on the examining table in the supine position, respiratory rate, pulse rate, blood pressure, pupil size and reaction to light as well as a subjective estimation of well-being were recorded. The volunteer was instructed to perform ten dry swallows (DS) and ten wet swallows (WS, 5 ml water), at 20 second intervals. The motility pattern was continuously recorded. After establishing baseline values for each subject either 0.2 mg morphine sulphate per kg body weight (ten subjects) or 1 c.c. saline (five subjects) was injected subcutaneously. Subjects in neither group were told

whether saline or morphine was to be given at the onset of the experiment. Oesophageal and LES recordings as well as clinical observations described above were made at 15, 30, 45, 60 and 75 minutes post injection. Each recorded value at these intervals is the mean of five dry or wet swallows.

Analysis of Data

The manometric tracings were independently evaluated by two of the investigators. They had no knowledge of whether saline or morphine had been given in the tracing they were assessing. Their interpretations did not significantly differ. As normal manometric data may show a considerable variation among individuals all data were analyzed versus basal values (=100%) using each subject as his own control. Student's t' -test was used for statistical calculations. Pearson product moment correlation coefficient was used to test association between two variables. Data are expressed as mean $\pm$ SEM.

RESULTS

Basal Data of 15 Subjects

The lower oesophageal sphincter was located on an average 44.6 to 49.2 cm from the nostrils giving a mean sphincter length of 4.6 ± 0.1 cm. The respiratory inversion point (RIP) was located at 46.6 ± 0.9 cm from the nostrils. LES pressure, expressed as the mean of three recordings, each via a separate tube, was

17.4 $\pm$ 1.1 mm Hg. The lower oesophageal sphincter relaxation in response to dry swallows was 88 $\pm$ 3% and in response to wet swallows 89 $\pm$ 2%. The propagation velocities after dry and wet swallows respectively were 6.2 $\pm$ 0.5 cm/sec and 4.3 $\pm$ 0.4 cm/sec. Oesophageal peristaltic wave amplitude was generally higher at the distal recording point irrespective of dry or wet swallows. Likewise, the duration of the complexes was longer in the distal position (Table I).

Table I

Basal oesophageal wave amplitude (mm Hg) and duration (sec) in response to dry (DS) or wet (WS) swallows.

Recording positions were 5.0 and 10.0 cm above the RIP.

Values are given as the mean of 10 dry and 10 wet swallows in each of 15 subjects and expressed as $\bar{X} \pm \text{SEM}$.

	5.0 cm (<u>Middle Orifice</u>)	10.0 cm (<u>Upper Orifice</u>)
Amplitude	DS 45 $\pm$ 6 WS 80 $\pm$ 12	37 $\pm$ 3 61 $\pm$ 12
Duration	DS 4.56 $\pm$ 0.25 WS 5.97 $\pm$ 0.63	4.15 $\pm$ 0.26 4.60 $\pm$ 0.38

Effect of morphine injection

Lower oesophageal sphincter pressure increased slightly, although not significantly, after subcutaneous injection of morphine (Table II). The relative relaxation of the sphincter decreased significantly with maximum effect appearing 30 minutes after the injection (Figure 3). Linear correlation of sphincter pressure versus relative relaxation revealed a regression coefficient for dry swallows of -0.88 and for wet swallows of -0.83 suggesting that the decreased relative relaxation at least partly, was due to the increased LES-pressure. Absolute relaxation, however, also decreased as shown in Table II. As can be seen the maximal relaxation in this respect appeared somewhat later and lasted longer than the relative relaxation. The amplitude of oesophageal waves increased slightly but insignificantly, 10.0 cm above RIP in response to wet swallows but were otherwise uninfluenced (Figure 4). Oesophageal wave amplitude was not influenced following dry swallows. Duration of the peristaltic waves and propagation velocity were not influenced by morphine (Data not shown). No significant changes were observed in heart rate, respiratory rate, systolic and diastolic blood pressure. All subjects showed pupillary constriction 30-45 minutes after morphine injection. They all experienced various degrees of light headedness and euphoria within 15 minutes and felt sleepy later on.

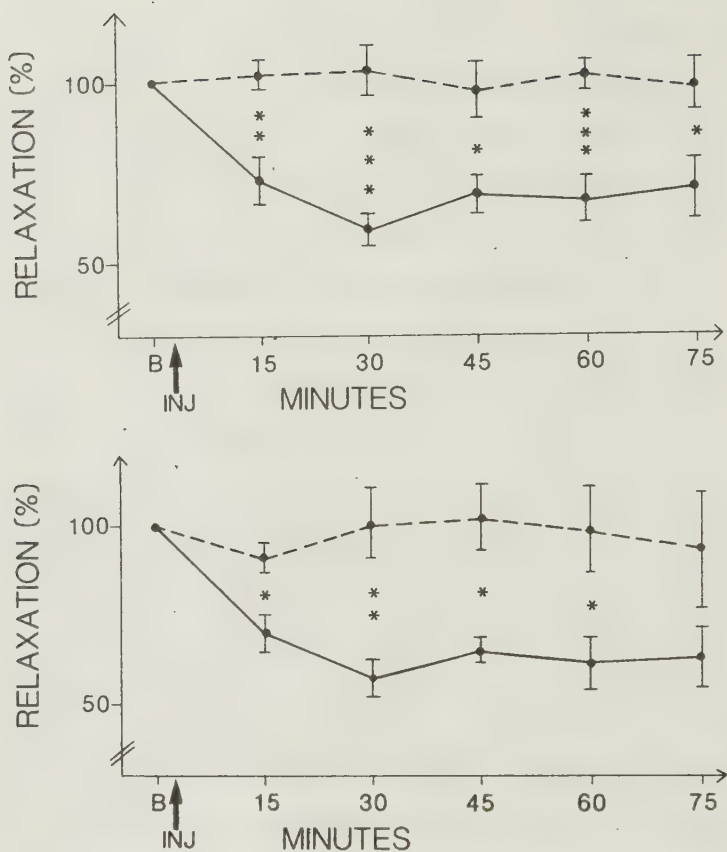


Figure 3. Lower esophageal sphincter (LES) relaxation expressed as percentage of LES pressure in response to wet swallows (Fig. 3a) and dry swallows (Fig. 3b) before (B) and after the injection of morphine (—) or saline (----). * denotes a p-value < 0.05, ** denotes a p-value < 0.01 and *** denotes a p-value < 0.001 when tested against basal values. Mean $\pm$ SEM. The saline data depicted in this figure are reproduced with kind permission from Surgical Gastroenterology (7).

Effects of saline injection

The manometric parameters studied were uninfluenced by the administration of saline during 75 minutes following the injections as reported in detail elsewhere (7) (Figure 3). No changes were observed in the clinical parameters.

Table II

Lower oesophageal sphincter pressure (LESP) and relaxation in response to dry (DS) and wet (WS) swallows before and after subcutaneous injection of morphine. (Mean $\pm$ SEM.) $n = 10$

	Before	15 min	30 min	45 min	60 min	75min
LESP	18.8 $\pm$ 2	20.6 $\pm$ 2.5	23.3 $\pm$ 3.4	22.0 $\pm$ 2.9	22.7 $\pm$ 1.6	23.8 $\pm$ 1.8
DS-Relax	16.9 $\pm$ 1.9	12.2 $\pm$ 2.4	10.5 $\pm$ 1.3*	11.0 $\pm$ 1.3	10.4 $\pm$ 1.5*	10.3 $\pm$ 1.4*
WS-Relax	16.7 $\pm$ 1.8	11.8 $\pm$ 1.3*	11.1 $\pm$ 1.1*	12.2 $\pm$ 1.9	12.7 $\pm$ 1.2	13.6 $\pm$ 2.2

*denotes p - value of < 0.05 when tested versus basal values

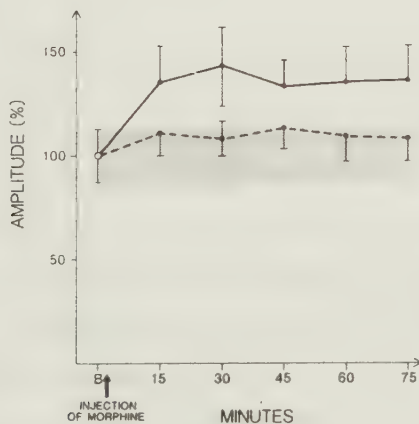


Figure 4. Oesophageal wave amplitude before (B) and after the injection of morphine as recorded 5.0 cm (---) and 10.0 cm (—) above the respiratory inversion point. Post-injection values are expressed as percentage of basal values ($B = 100$). Mean $\pm$ SEM. Shaded area represents basal ($B \pm$ SEM) amplitude.

DISCUSSION

Until recently it was assumed that the motility of the oesophagus and the gastroesophageal sphincter was regulated mainly by the sympathetic and parasympathetic nervous system. In addition, the role of gastrointestinal hormones, especially gastrin, and certain substances such as alcohol and coffee has been discussed in this respect. Enkephalins representing a subgroup of endorphins are found in high concentrations in neurons of the myenteric plexus of all parts of the gastrointestinal tract (8). They are known to act as neurotransmitters and possibly as circulating hormones, too. In the oesophagus and lower oesophageal sphincter (LES) enkephalin containing cell bodies are found abundantly. Their processes are part of the myenteric plexus which innervates the muscularis mucosa. Five distinct types of opioid receptors have been demonstrated in lower oesophageal sphincter of opossum (3). Activation of three of these (μ , κ and a specific mepiridine binding) cause inhibition whereas stimulation of the remaining two (σ and δ) result in contraction of LES. Demonstration of these receptors as well as the presence of opioid containing neurons in the myenteric plexus suggest that opioids play a role in the physiological regulation of lower oesophagus and LES. In an extensive study of a group of patients with esophageal motility disorders Benjamin et al (9) tested edrophonium, bethanechol and pentagastrin as provocative drugs to reproduce the clinical symptomatology but did not consider endorphins. However, Stacher et al (6) investigated the influence of a methionine enkephalin

analogue, FK 33-824 on oesophageal motility of nine normal volunteers and reported an increase in amplitude and duration of peristaltic waves in the distal one-third of the oesophagus in a dose-dependent fashion. They postulated that enkephalins play an excitatory role on the smooth muscle by blocking the inhibitory impulses. In earlier studies others (10, 11) examined the influence of morphine and meperidine (Pethidine) on LES function. Hall et al (10) in an earlier study from our laboratory demonstrated a decrease in the pressure of LES under the influence of morphine which increased the probability of gastro-oesophageal reflux. Similar results were obtained by Hey et al (11) who found a slight dose dependent decrease of LES-pressure after i.m. Pethidine. The effects were abolished by i.v. metoclopramide.

Our study demonstrated that parenteral injection of 0.2 mg per kilogram body weight of morphine into healthy young adults significantly inhibited the relaxation of LES. The effect was maximal at 30 minutes and was still present to a lesser degree at 75 minutes after the injection (Figure 3). In the distal one-third of the oesophagus the deglutative waves showed slight increase in magnitude but no change in duration or propagation velocity of waves between the two recording orifices situated 5.0 and 10.0 cm above the RIP. This may either be a direct influence of morphine on smooth muscle of the distal oesophagus or a compensatory response of the oesophagus to overcome a non-

relaxing sphincter. The inhibitory effect on LES relaxation was totally absent in the five subjects who were injected with saline (7) (Figure 3).

The divergent results of the present study when compared to others (6, 10, 11) may be explained by pharmacological differences of the administered substances. As indicated above there are opioid receptors of different qualities in LES. Activation of these may thus result in stimulatory or inhibitory effects and furthermore, these effects may be dose dependent. Future studies should be done to clarify this. Another explanation is that somewhat different manometric techniques were used in the previous studies during which rapid pull through technique was employed. The currently used method is superior, well established and known to give reproducible results.

Failure of LES to relax completely under the influence of morphine in normal subjects as demonstrated in our study is theoretically comparable to a situation which is found in achalasia. In their experiment, Stacher et al (6) observed a similar effect of FK 33-824, a methionine enkephaline analogue on the force of peristaltic waves in the distal part of oesophagus as we did following injection of morphine. It is therefore possible that excessive autonomous secretion of endogenous enkephalins and subsequent stimulation of specific receptors in oesophagus or LES could result in some of the hitherto obscure non-specific oesophageal motility disorders. The use of enkepha-

lin analogues and morphine as well as their antagonists may therefore be of value as provocative or blocking pharmacological agents during manometric examinations of such conditions. With the availability of sophisticated pneumohydraulic capillary infusion system and application of recent information on neurotransmitters it could be possible to elucidate some of the unresolved clinical diagnoses of oesophageal pain and dysphagia.

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Barrett's Esophagus

Comparison of Benign and Malignant Cases

DAVID B. SKINNER, M.D., BRUNO C. WALTHER, M.D., ROBERT H. RIDDELL, M.D., HELMUT SCHMIDT, M.D.,
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Using strict criteria for diagnosis, 23 patients having benign Barrett's esophagus, and 20 patients with adenocarcinoma arising in this epithelium have been analyzed. Evidence supports severe gastroesophageal reflux as a cause of Barrett's esophagus. Successful antireflux surgery leads to stabilization and possibly regression of the dysplasia in Barrett's epithelium, and can be followed by squamous epithelial regeneration in some. Antireflux surgery is advocated in all patients with Barrett's esophagus demonstrated to have abnormal reflux regardless of symptoms. The malignant potential of the columnar epithelium is higher in men who smoke, in patients with intestinal-type metaplasia who continue to have severe reflux, and in patients who develop dysplasia. In those with high grade dysplasia, the probability of carcinoma is high and esophagectomy should be seriously considered in the hopes that the pathological stage of the neoplasm is still favorable.

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IN 1950, BARRETT DESCRIBED the condition of peptic ulceration in the esophagus arising in a zone of gastric-type epithelium.¹ Allison and Johnstone, in 1953, published additional cases in which the esophagus was lined with gastric-like mucosa and suggested the term "esophagus lined with columnar epithelium."² Barrett accepted this terminology and provided a more complete description of the disease in 1957.³ Controversy has persisted to the present concerning the etiology, definition and classification, complications, and clinical management of Barrett's esophagus.⁴

The etiology of the columnar-lined esophagus has

been debated extensively. Among the original descriptions of the condition, Barrett proposed a congenital origin, whereas Allison and Johnstone indicated the possibility that the condition might be acquired. Descriptions of a cephalad migration of peptic esophagitis and stricture above an ascending boundary of a columnar-lined esophagus as in the cases of Goldman and Beckman,⁵ and Mossberg⁶ provided strong evidence that the condition could be progressive and result from persisting severe gastroesophageal reflux and complicating esophagitis. The concept of erosive reflux esophagitis healing by upward migration of adjacent columnar epithelium was advanced by Hayward in 1961.⁷ The possibility of repair by extension from esophageal glands following reflux esophagitis was proposed by Adler in 1963.⁸ It is now widely accepted that a substantial proportion of patients with Barrett's esophagus do have severe gastroesophageal reflux.

Almost simultaneously with the reporting of the benign version of this condition, cases were described in which adenocarcinoma of the esophagus developed in the aberrant gastric-type mucosa, the first being described by Morson and Belcher in 1953,⁹ and in this country by McCorkle and Blades in 1955.¹⁰ Although the potential for the columnar-lined esophagus to undergo malignant degeneration has become well known, the interrelationships between the benign and malignant form of the disease, and potential for progression from one to the other, have been poorly understood. The role of persisting reflux in causing progression of the condition towards malignant degeneration has been uncer-

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tain, and the effect of correcting the reflux on the fate of the columnar-lined epithelium has remained unclear.

The purposes of this study are to compare cases with the benign or malignant type of columnar-lined esophagus to detect differences between the two groups which might suggest etiological or prognostic factors. The fate of the epithelium in benign cases after successful anti-reflux repair is examined to detect evidence of regression or change in the type or degree of dysplasia in the epithelium. Based upon results achieved in the benign and malignant cases, suggestions are made concerning treatment.

Definitions

For comparisons among patients with Barrett's esophagus to be meaningful, precise definitions of the abnormality prove necessary. For the purposes of this study, Barrett's esophagus is the condition in which 3 or more cm of the distal tubular esophagus are lined by columnar-type epithelium. This definition is deliberately chosen, recognizing that the squamo-columnar junction may be irregular, and that the distal 1–2 cm of normal tubular esophagus are lined with cardia-type columnar epithelium. Equivocal cases or patients with only small tongues of columnar epithelium are thereby excluded. The definition requires that the 3 or more cm of columnar epithelium occur within the tubular esophagus, regardless of the presence or absence of a hiatal hernia (Fig. 1). The tubular esophagus in cases of hiatal hernia is defined as that segment of foregut which participates in esophageal peristaltic contractions, as are seen during endoscopy or barium swallow, and recorded during manometric studies.

The malignant version of Barrett's esophagus is defined as the condition in which adenocarcinoma occurs above the junction of the tubular esophagus with stomach, and in which mucosa adjacent to the carcinoma demonstrates columnar epithelium, meeting the above definition of Barrett's esophagus.

For the purposes of this study, two cases of carcinoma arising in ectopic gastric-type epithelium occurring in the cervical esophagus above a zone of confluent squamous epithelium are not considered in the analysis. The etiology in such cases appears to be congenital,¹¹ and not necessarily related to the apparent reflux-induced cause of Barrett's epithelium in continuity with the cardia and gastric mucosa.

Patient Population

The records of the Esophageal Laboratory in the Department of Surgery at the University of Chicago Medical Center between the yrs 1974–82 were reviewed to identify patients with either benign or malignant types of Barrett's esophagus. Based upon radiographic, endoscopic, or biopsy material, 29 patients had been seen who were initially identified as having benign Barrett's esophagus. Among these, 23 were accepted as meeting the stringent definition described above and having the condition proved by biopsies of columnar epithelium more than 3 cm above the junction of tubular esophagus with stomach. Six cases were excluded because of uncertainty as to the location of biopsies or endoscopic findings. Additional cases in which columnar epithelium extended into the esophagus after esophagectomy and esophagogastrostomy were also excluded.

During the same time, 29 patients were seen with

Barrett's Esophagus Barrett's Esophagus and Hiatal hernia Barrett's Esophagus and adenocarcinoma

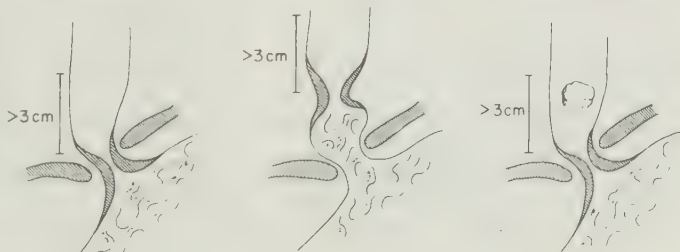


FIG. 1. Diagrams illustrating the definitions of benign and malignant epithelium. Regardless of the presence of a hiatal hernia, the columnar lining of the tubular esophagus must extend at least 3 cm above the junction with the stomach.

adenocarcinoma of the esophagus in whom the cancer was suspected after surgery to arise from Barrett's epithelium. Among these, 20 cases were accepted as meeting the definition of adenocarcinoma arising in Barrett's epithelium following detailed analysis of the pathological specimens. Using these precise definitions, the clinical records of the 23 patients having benign Barrett's esophagus were compared with the clinical data among 20 patients having adenocarcinoma arising in an esophagus which had benign Barrett's epithelium elsewhere in the specimen.

Statistical Method

For comparison of measurements between different groups, a normal probability plot was performed. When the data was not normally distributed, the Mann-Whitney nonparametric test was used, otherwise Student's *t*-test for unpaired data was applied. In each evaluation, both the *t*-test and Mann-Whitney were performed, and in every evaluation they gave the same results concerning significance. For nominal data, the chi square test was used when the total of the table was more than 40. For smaller numbers, Fisher's exact probability test has been applied.¹²

Comparisons of Benign and Malignant Cases

Age, sex, race, and habits. Among the 23 patients with benign columnar lining in the esophagus, the mean age was 52 yrs (range 13–78) and the median age was 55. Among the malignant group, the average of 60 yrs (range 45–78) was older ($p = .052$ by Student's *t*-test), but the median age of 59.5 yrs was not significantly different from the benign group (Mann-Whitney nonparametric test).

Barrett's esophagus was observed in 9 women and 34 men. The incidence of malignancy was high among men, as 18 of the 20 cases of cancer occurred in men compared to 16 of 23 benign cases being in men ($p = 0.1$).

Barrett's esophagus was a disease occurring overwhelmingly in white patients. All 20 cases of definite malignant Barrett's esophagus, and all 9 of the additional cases considered as possible malignant Barrett's esophagus but excluded based on pathological analysis, occurred in Caucasians. Among the benign cases, 21 occurred in whites and 2 in blacks; all 6 patients excluded as not meeting the stringent definition were also white. This predominance of the disease in white patients was in contrast to the racial mixture of our overall surgical patient population which has been approximately one-third black, and our patients with squamous

cell carcinoma of the esophagus, 30% of whom were black.

In reviewing social habits, 10 of 23 patients with benign Barrett's esophagus had a smoking history. Among the malignant group, the incidence of smoking was greater, in that 16 out of 20 smoked two or more packs per day ($p < .025$). Among the male patients, the correlation of smoking with malignancy was even more striking in that 16 of 18 men with cancer smoked, compared to 8 of 16 with benign Barrett's ($p < .025$).

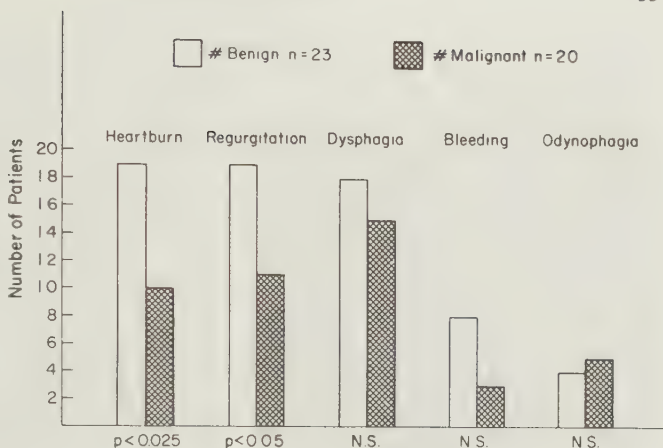
Alcoholic beverages were ingested "socially" or more regularly by ten people having benign Barrett's esophagus, and by 13 in the malignant group. The difference was not significant.

Symptoms. The important role of gastroesophageal reflux in Barrett's esophagus was indicated by the observation that all but 2 of the 23 patients with benign Barrett's complained of either heartburn or regurgitation aggravated by postural change. In addition, 18 of the benign cases experienced dysphagia, 8 had upper gastrointestinal bleeding, and 4 had odynophagia. Among the malignant group, 13 out of 20 complained of heartburn and/or regurgitation, but the frequency of these symptoms was significantly less ($p < .05$) than in the benign group (Fig. 2). In the cancer group, 15 complained of dysphagia, 3 bleeding, and 5 odynophagia. The length of the history of esophageal complaints varied from 5 months to 29 yrs in the benign group (mean 12, median 10 yrs). This did not differ significantly from the duration of history of esophageal disorder in patients with malignant disease, which varied from 0 to 40 yrs with a mean of 8.7 yrs and median of 2 yrs.

Radiology. A hiatal hernia was identified radiographically in 20 of the 23 patients with benign disease and in 16 of 20 with malignant disease. In the latter group, assessment of the hiatus could not be made in two because of the obstruction caused by the tumor. A stricture was identified by the radiologist during barium swallow in 14 of 23 patients with benign disease and in 6 of 20 with malignant disease. A mass or narrowing, suggesting carcinoma, was seen in 11 patients. Three patients having adenocarcinoma had neither stricture nor mass seen radiographically. Among the benign cases, an esophageal ulcer was observed in 9 patients. Except for the presence of a bulky tumor mass in some of the malignant cases, radiologists could not differentiate with certainty between patients with Barrett's esophagus having benign or malignant epithelium. In patients without either ulcer or stricture, the diagnosis was frequently not made at all.

Esophageal function tests. Twenty-two of the 23 patients with benign Barrett's epithelium were studied

FIG. 2. The frequency of esophageal symptoms among the 23 patients with benign and 20 patients with malignant Barrett's esophagus are shown. Differences in heartburn and regurgitation are significant by the chi square test.



prior to treatment in our hospital by esophageal manometry, and pH acid reflux tests including 24 hr pH monitoring in 21.¹³ In one patient, a tight stricture precluded preoperative testing. Based on these studies, abnormal gastroesophageal reflux was identified in 19 patients. No significant reflux was measured by the 24 hr pH test in two patients, one of whom had had a previous vagotomy and stricture, and another, who was referred after a successful antireflux repair elsewhere. The former did have abnormal reflux during the Standard Acid Reflux pH Test (SART).¹⁴ The details of the manometric and pH study abnormalities in our patients having benign Barrett's esophagus have been reported. This documented a severe disorder in the mechanics of the distal esophageal high pressure zone, frequency of abnormal reflux, and acid clearing from the esophagus.¹⁵ Esophageal function tests could be performed in three of the malignant group and documented abnormal reflux in each. Four other patients showed free reflux on barium swallow.

Type of epithelium. In the columnar-lined esophagus, three distinct types of epithelium were seen and were similar to those described by Paull, et al.:¹⁶ a fundic type (FT) in which parietal cells and chief cells were present (Fig. 3); a junctional or cardia type (CT) having mucous secreting columnar cells and often pyloric-type glands (Fig. 4); and a third type of distinctive specialized columnar epithelium, showing intestinal-type metaplasia

(IT) indicated by the presence of goblet cells and which sometimes contained pyloric glands (Fig. 5). Among the benign cases, pathological material for review included from 1-6 biopsies obtained more than 3 cm proximal to the junction of the tubular esophagus with stomach. In 17 of the 23 patients, such biopsies showed the specialized intestinal type (IT) of epithelium (Table 1). CT was identified in 14 and FT in eight. No patients had only FT epithelium in the biopsies, but this type was

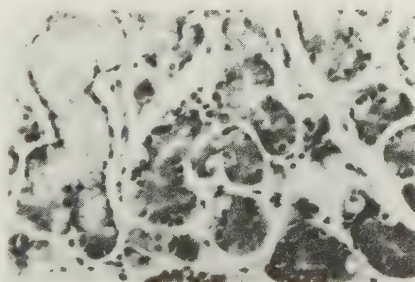


FIG. 3. Fundic type of epithelium in Barrett's esophagus. Note the darker staining chief cells, paler staining parietal cells and clear mucin producing cells seen primarily on the left ($\times 800$).

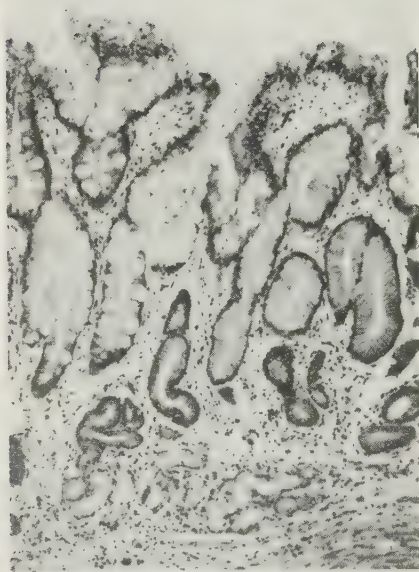


FIG. 4. Cardia type of epithelium in Barrett's esophagus (right) contrasted with intestinal mucosa (left). Note the pyloric glands in the lower part of the figure ($\times 100$).



FIG. 5. Intestinal type metaplasia in Barrett's esophagus. Note the mucin depletion in the crypt on the right, the nuclei of which are enlarged, hyperchromatic, and may represent the earliest stages of neoplastic transformation. However, as this falls short of unequivocal dysplasia, it is categorized as indefinite for dysplasia, unknown ($\times 300$).

TABLE 1. *Types of Epithelium in Barrett's Esophagus*

	Benign	Malignant
IT*	7	12
CT†	4	0
FT‡	0	0
IT + CT	4	6
IT + CT	2	0
CT + FT	2	0
IT + CT + FT	4	2

*IT = intestinal type. †CT = cardia type. ‡FT = fundic type.

found in association with IT in two patients, CT in two patients, and all three cell types were present in four patients.

Among the malignant cases in which more thorough pathological examination could be made in the resected specimens, IT epithelium was identified in all 20 specimens, CT in the tubular esophagus 3 or more cm above the junction in eight specimens, and FT in two. In 12 of the specimens, IT was the only type epithelium identified, IT and CT were found together in six, and all three types were identified in two specimens. There were no significant differences in the patterns of epithelium identified between the benign and malignant cases. It appeared that the specialized intestinal type epithelium, featuring goblet cells, was the hallmark of Barrett's esophagus, particularly in patients at risk to develop carcinoma.

Epithelial dysplasia. All biopsies and resected specimens were carefully reviewed to identify dysplasia in the Barrett's epithelium. Dysplasia was defined as being "an unequivocal neoplastic alteration of the glandular (columnar-lined) esophagus." It should be stressed that such dysplastic epithelium might not only be a marker or precursor of carcinoma, but might itself be malignant and associated with direct invasion into the underlying tissue. Dysplasia was graded (Table 2) using the criteria established for inflammatory bowel disease.¹⁷ Mucosa was scored as negative for dysplasia if the nuclear changes of the metaplastic epithelium were similar to those found in the same epithelium in its normal ana-

TABLE 2. *Classification of Dysplasia in the Mucosa of "Barrett's" Epithelium*

Negative for dysplasia
Indefinite for dysplasia
a) Probably negative
b) Unknown
c) Probably positive
Positive for dysplasia
a) Low grade
b) High grade

tomic location (*e.g.*, stomach, intestine). Actively regenerating epithelium was considered to be negative for dysplasia. If dysplastic nuclei were largely confined to the basal parts of the cells, it was arbitrarily called low grade (Fig. 6). More severe changes with nuclei regularly approaching the upper pole of the cells and all changes, up to and including carcinoma *in situ*, were called high grade (Fig. 7). All epithelia not falling into either unequivocally positive or unequivocally negative were graded as indefinite for dysplasia. Within this category, changes thought most likely to represent the results of active inflammation were termed 'indefinite for dysplasia, probably negative,' if most likely but not unequivocally to represent a neoplastic process they were termed 'indefinite for dysplasia, probably positive.' Remaining biopsies were categorized as 'indefinite for dysplasia, unknown.' When a series of changes, or multiple biopsies were encountered showing more than one of these categories, the most severe was utilized.

Among the biopsies from the 23 benign cases, definite low grade dysplasia was present in two with IT epithelium. In one patient with a stricture, this was treated by esophagectomy and colon interposition. The second patient refused esophagectomy and underwent a Belsey Mark IV anti-reflux repair. Biopsies obtained 7 yrs later showed only changes indefinite for dysplasia based upon inspection of 8 biopsies. Five other benign cases had biopsies showing indefinite, probably negative criteria for dysplasia, four in IT, and one in FT epithelium.

In the malignant cases, zones of benign Barrett's epithelium were found in all resected specimens. Dysplasia of high grade was found in IT epithelium in seven specimens, low grade dysplasia in IT of nine specimens, and no dysplasia in the Barrett's epithelium was noted adjacent to the adenocarcinoma in four specimens. The high incidence of dysplasia in the IT epithelium among the malignant cases compared to the benign cases underscored the seriousness with which dysplasia should be taken as a predictor of malignant degeneration in Barrett's epithelium.

Among the 18 patients in whom definite low grade or high grade dysplasia was seen, 16 had adenocarcinoma. In three patients undergoing esophagectomy, dysplasia, but not frank carcinoma, was found in the preoperative biopsies. Two of these patients had invasive carcinoma in the resected specimen, and one of these had a positive esophageal cytology. In one additional case of ectopic gastric epithelium in the cervical esophagus, not in this series, a preoperative biopsy showed only dysplasia in IT epithelium, but the resected specimen showed microinvasive carcinoma. Dysplasia was the most serious indicator of potential malignant degeneration in Barrett's epithelium, and was particularly associated with the intestinalized type of epithelium.

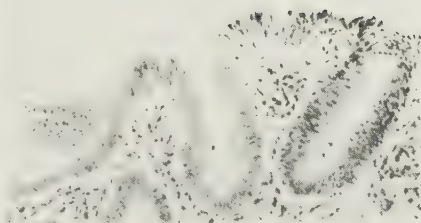


FIG. 6. Low grade dysplasia in Barrett's epithelium. Compared with the crypt in Fig. 5, the nuclei are uniformly enlarged, hyperchromatic and there is marked mucin depletion. Nuclei are largely confined to the cell bases, hence the categorization of low grade dysplasia ($\times 80$).

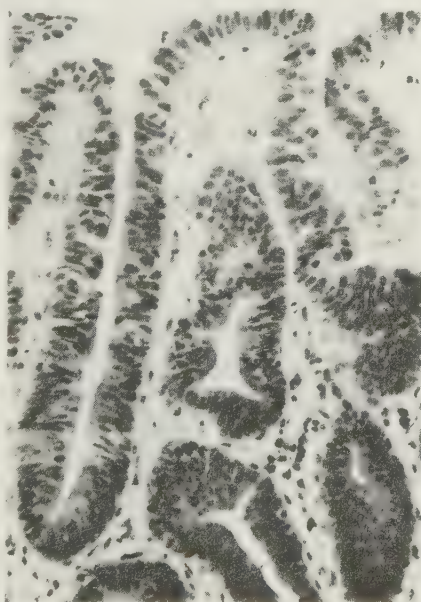


FIG. 7. High grade dysplasia in Barrett's epithelium. Compared to Fig. 6, the neoplastic nuclei regularly reach the upper part of the cells ($\times 80$).

Treatment: Benign Cases

Anti-reflux repair. From the 23 benign cases, 13 patients were selected for treatment by anti-reflux repair, nine of whom had the Belsey Mark IV procedure¹⁸ and four who had the Nissen fundoplication operation.¹⁹ In all but one, the operation was performed through a left thoracotomy so that the entire esophagus could be inspected, and lymph nodes sampled as a further precaution against missing malignant disease. Three of these patients had undergone previous unsuccessful antireflux surgery. Eight had a stricture requiring preoperative dilatations, and five had an ulcer in the Barrett's epithelium. Of these 13 patients, 12 have been followed to date and ten have recently been restudied by esophageal function tests, radiography, and esophagoscopy with multiple biopsies. These evaluations were done from 2–7 yrs after surgery (mean 4 yrs). One patient moved away and has been lost to follow-up, one was asymptomatic and deferred testing, and one has been evaluated symptomatically to have a recurrence, but has not yet agreed to restudy. Symptomatically, the results of antireflux surgery are shown in

Fig. 8. Eleven out of twelve are asymptomatic or have only minimal heartburn or regurgitation.

Compared to preoperative values, the follow-up function tests showed a significant increase in distal esophageal segment (DES) pressure from a mean of 4.4 mmHg to 12.4 mmHg ($p < .001$). Before operation, no patient had DES pressure above 9 mmHg, and after antireflux surgery, nine of ten patients had a DES pressure greater than 9 mmHg. Length of the DES high pressure zone did not change significantly after operation. Reflux measured by both the Standard Acid Reflux Test and 24 hr pH monitoring demonstrated that the frequency and duration of reflux was reduced to normal in eight of ten patients after surgery (Fig. 9). Two patients were completely asymptomatic, but had abnormal frequency and duration of reflux 4 and 7 yrs after Belsey repairs. The SART was positive in each. In each, a stricture and ulcer seen after surgery had healed completely.

By visual endoscopic inspection and biopsies, the location of the junction of squamous and Barrett's epithelium has remained unchanged in eight patients. In two, the junction was found to be 4 and 5 cm distal to

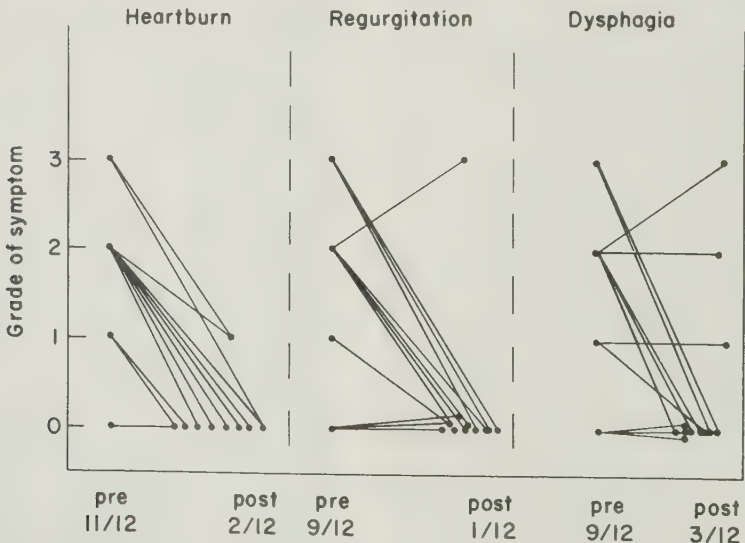


FIG. 8. Comparison of symptoms before and 2–7 yrs after antireflux surgery in 12 patients. The one highly symptomatic patient has thus far refused confirmatory esophageal function tests.

the preoperative level when endoscopy was repeated within 1 yr of operation. These changes confirmed by biopsy were thought due to surgical relocation of the esophagus rather than regression of the Barrett's process. On a second postoperative endoscopy 2 yrs after operation, no Barrett's epithelium was identified by biopsy in one of these patients.

Extension of patchy zones of squamous epithelium into regions of previously columnar-lined esophagus was seen in two patients. By visual endoscopic examination, this regenerating squamous epithelium appeared as distinct thin patches of opaque epithelium overlying the reddened residual columnar epithelium. This was confirmed by multiple biopsies which showed superficial normal squamous epithelium with residual glandular epithelium beneath (Fig. 10). To our knowledge, this has not been described previously. In both patients, reflux had been totally corrected by Belsey antireflux repairs. One patient was a nonsmoker, the other had stopped smoking at the time of his antireflux procedure.

Among five patients with no dysplasia on preoperative biopsies, four still showed no dysplasia, but one asymptomatic patient with positive reflux tests progressed from no dysplasia to an indefinite, probably negative grade of dysplasia. Of the four patients with indefinite, probably negative dysplasia before surgery, three have had their reflux corrected and two continued to have indefinite dysplasia in postoperative biopsies, while one now has no dysplasia. The fourth who has persistent asymptomatic reflux and continues to smoke has progressed to low grade dysplasia 4 yrs after surgery. The one patient with low grade dysplasia before a successful antireflux repair has shown an indefinite, probably positive status 7 yrs later.

Esophagectomy. Four patients were selected for esophagectomy and isoperistaltic left colon interposition.²⁰ In one, the indication was a deep penetrating Barrett's ulcer into the mediastinum, and in three the indication was stricture, complicated by dysplasia in one and by two previous antireflux repairs in a second. All four patients had an excellent functional result with follow-ups of 2, 2, 4, and 5 yrs. One patient died recently of a cerebral vascular accident 5 yrs after colon interposition but was eating well until his stroke. One patient developed an ulceration at the gastro-colonic anastomosis requiring revision 3 yrs after colon interposition, but recovered fully and resumed eating normally.

No operation. Six patients did not undergo surgery. In three, the decision was made because of other illnesses, including lung cancer, recent stroke, and acute psychosis. None had dysplasia on biopsy. One patient was referred after a successful Belsey antireflux repair

24 Hour Esophageal pH Monitoring

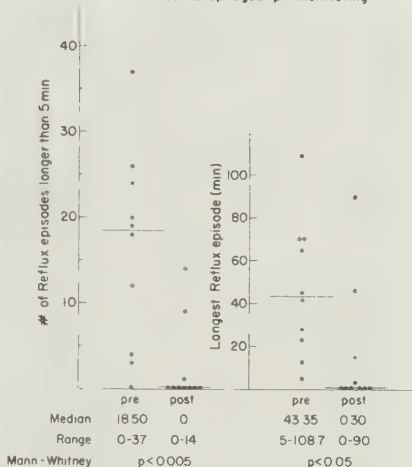


FIG. 9. Comparison of measurements of reflux by 24 hr pH monitoring before and 2-7 years after antireflux surgery in ten patients.

and has remained under observation. No dysplasia was seen in biopsies. Two patients refused operation because of minimal symptoms. In one of these, the Barrett's epithelium has progressed from an indefinite, probably negative status to high grade dysplasia during 3 yrs of observation on medical treatment (Fig. 11). He has con-

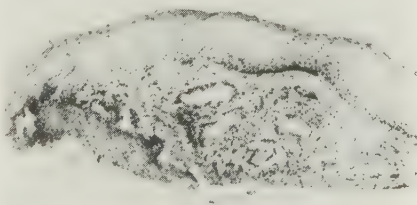


FIG. 10. Endoscopic biopsy taken 2 yrs after surgery from a region previously lined with intestinal type metaplasia. Squamous epithelium is overlying the residual Barrett's epithelium ($\times 100$).

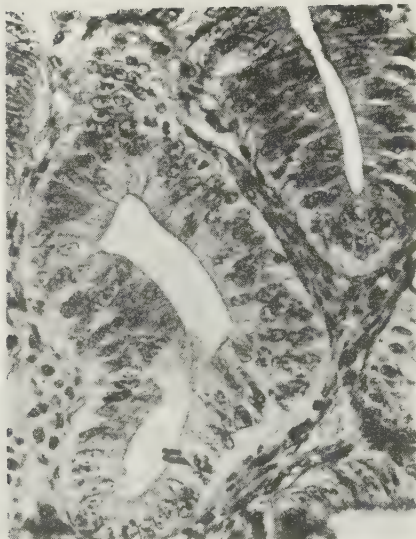


FIG. 11. High grade dysplasia that evolved over a 3 yr period in a patient who smoked heavily but had only minimal reflux symptoms ($\times 500$)

tinued smoking, and operation has been strongly advised. The other patient did not have dysplasia and has remained asymptomatic after 4 yrs, but has not been re-evaluated.

Treatment: Malignant Cases

All 20 patients with malignant Barrett's esophagus underwent resection. In 16, a radical *en bloc* resection of the mediastinum was performed,²¹ and in four, palliative operations were undertaken because of concomitant cardiovascular disease in two, obvious extension of disease in one, and the surgeon's choice in one case. Among the 16 patients undergoing radical resection, there were two deaths in hospital within 30 days, and five additional patients died within the first 6 mths, two from pneumonia, one from a late subphrenic abscess, and two from metastatic cancer. Four patients remained living and well without evident disease at 9 mths, 2 yrs, 2½ yrs, and 8 yrs after radical esophagectomy. The survival curve by actuarial analysis in the

patients undergoing radical *en bloc* esophagectomy for adenocarcinoma arising in Barrett's esophagus has not varied significantly from the survival curve in 78 other patients undergoing the same operation for other types of esophageal carcinoma. Among the total group of patients undergoing *en bloc* resection for esophageal neoplasms, the 5 yr survival determined by actuarial table analysis was 22%. Among the four patients undergoing palliative resections, three died of cardiovascular complications within the first 30 days after operation, and one died 14 months after surgery from metastases.

Previous analysis of esophagectomy specimens containing carcinoma has demonstrated that spread to lymph nodes or full thickness wall penetration were the two most significant factors determining prognosis.²² Among the 16 patients undergoing radical *en bloc* resection, five had no positive lymph nodes, and three have survived over 2 yrs without evident disease. One died of an early myocardial infarction, and the second died of pneumonia and respiratory failure 6 wks after surgery. Five patients had no esophageal wall penetration, including the three long-term survivors, and the patient with negative lymph nodes who died from pneumonia. The fifth patient in this group had five positive lymph nodes and died of widely disseminated cancer within 3 months. The combination of both negative lymph nodes and lack of wall penetration appeared to be significant in predicting long-term survival after successful operations for cancer arising in Barrett's esophagus, as in other types of esophageal carcinoma. The dismal results in patients with more advanced disease stressed the importance of close follow-up in patients having benign Barrett's esophagus, and the necessity of treating patients with dysplasia aggressively.

Discussion

Barrett's esophagus is no longer a medical rarity or curiosity. To permit comparison of data among various series, more precise descriptions of the condition are desirable. Previous reports do not specify an exact definition. The definitions proposed and used in this report acknowledge that the squamo-columnar junction may be irregular, and that columnar epithelium of the cardia type extends upwards into the tubular esophagus for 1–2 cm. The squamo-columnar junction is situated within, or just proximal to the competent distal esophageal sphincter mechanism seen endoscopically when the esophagus is dilated by insufflation of air. Observation of the squamo-columnar junction at this level is not abnormal nor indicative of Barrett's esophagus. A 3 cm zone of columnar epithelium is utilized to ensure that

no equivocal cases are included. Measurement of more than 3 cm of columnar epithelium lining the tubular esophagus is a more precise definition than the measurement of the squamo-columnar junction in centimeters from the incisor teeth. When the latter determination is used, a large hiatal hernia may lead to proximal displacement of the squamo-columnar junction, even in the absence of Barrett's epithelium. The use of a precise definition may reduce some of the confusion in reports of this condition.

The high incidence of severe gastroesophageal reflux documented in the benign cases in this series confirms many other reports which show a high incidence of hiatal hernia and reflux in Barrett's esophagus. Our previous report of greater severity of reflux in Barrett's esophagus cases, compared to results of reflux testing in patients with ulcerative esophagitis but without Barrett's epithelium indicates that the Barrett's cases have a more advanced abnormality of the cardia and acid clearance.¹⁵ This data adds further evidence to the likelihood that pathological reflux is a cause of Barrett's esophagus. The experimental data of Bremner, Lynch, and Ellis points to reflux causing columnar transformation of injured mucosa.²³ The report of Hamilton and Yardley of Barrett's epithelium developing proximal to esophagogastric anastomoses after esophagectomy in patients with post-operative reflux further suggests this etiology.²⁴ Although not reported in this series, similar findings after esophagogastricostomy are seen in some of our cases.

The absence of symptomatic heartburn and regurgitation does not exclude pathological reflux in patients with Barrett's esophagus. It is well known that there are marked individual differences in sensitivity to reflux, and that patterns of reflux vary in different patients.²⁵ Persistent severe reflux in two of our postoperative cases who are asymptomatic suggests that Barrett's epithelium may not be sensitive to acid after ulceration or strictures heal. As compared to patients with reflux esophagitis without Barrett's epithelium in our earlier report, patients with benign Barrett's have less severe symptoms of heartburn and regurgitation in spite of significantly greater duration of acid reflux in the distal esophagus.¹⁵ This lack of correlation between symptoms and reflux emphasizes the importance of objective measurements of reflux in Barrett's esophagus cases by a method such as one of the esophageal pH reflux tests.

These data suggest that the malignant degeneration of Barrett's esophagus occurs in the presence of continuing reflux and persistent smoking. All three patients with invasive carcinoma without a stricture or large tumor mass studied by pH testing show severe reflux. Thirteen of the 20 malignant cases complained of heartburn

and regurgitation, and the incidence of hiatal hernia is similar to that in the benign cases. Of particular importance are the follow-up studies which demonstrate progression to dysplasia in three patients who have continued reflux in spite of surgical or medical therapy and who continued to smoke; two of these patients are asymptomatic and one has minimal symptoms. This suggests that persistent reflux can lead to development of dysplasia in the absence of symptoms of heartburn and regurgitation, a change that seems to be potentiated by smoking. It suggests an explanation for the lack of reflux symptoms before the onset of dysphagia in some of the patients developing cancer. A corollary is found in one patient having low grade dysplasia after surgery who had a successful antireflux operation and gave up smoking. Multiple biopsies have failed to confirm his dysplasia. These findings suggest that the combination of a successful antireflux procedure and cessation of smoking may be effective in preventing the subsequent development of dysplasia and carcinoma.

The importance of reflux is underscored by the observation that dysplasia does not progress or regress in all eight patients in whom reflux is documented to be corrected by pH studies after successful antireflux surgery. Since the two patients with continuing reflux and progressive dysplasia after antireflux surgery are as asymptomatic as those with successful repairs, the need for follow-up after surgery by quantitative measurements of reflux by pH studies is apparent. The lack of such studies may explain the occasional case reports in which carcinoma develops at a later time, following an apparently successful antireflux repair.

The 46% incidence of malignancy in this series is the highest reported. Although there are few papers published which provide a basis for judging incidence of carcinoma in Barrett's esophagus, the most common estimates are approximately a 10% risk of malignant degeneration.²⁶ In a large series, Naef, et al. describe 12 cases of adenocarcinoma arising among 140 patients with documented Barrett's esophagus, an incidence of 8.6%.²⁷ However, two other reports describe a higher incidence comparable to that which we observe. Radigan, et al. report 5 of 19 (26%) patients with Barrett's esophagus have adenocarcinoma.²⁸ Dees, Van Blankenstein, and Frenkel describe 13 cases of adenocarcinoma arising in Barrett's esophagus, and approximately 32 cases of benign Barrett's esophagus among 5,300 endoscopies carried out in Rotterdam.²⁹ This is an incidence of approximately 30% malignancy in Barrett's esophagus cases. The incidence of cancer in our laboratory is probably higher than the overall incidence in the population of Barrett's esophagus, since ours is a

surgical laboratory and it can be expected that only the more symptomatic patients are those referred. In a referral practice from a broad and ill-defined base, the total number of Barrett's esophagus patients in the population from which the adenocarcinomas are referred cannot be stated. The high incidence of stricture and ulceration in our benign Barrett's cases points to the selected nature of these cases.

Several other risk factors for development of carcinoma are identified in this series. The higher proportion of men than women developing adenocarcinoma in Barrett's esophagus is noted by Berardi and Devaiah, who find that approximately two-thirds of all cases reported in the literature occur in males.⁴ Haggitt, et al. observe 8 out of 12 cases of Barrett's adenocarcinoma in men.³⁰ The median age of 59.5 yrs in our cases corresponds exactly with the average ages of 58 and 60 in other reports.^{4,30} Our patients have an average duration of symptoms of 8.7 yrs compared to an average of 7.6 yrs in Berardi and Devaiah's review of the literature.⁴ The association with smoking is not reported previously, to our knowledge.

The type of epithelium found in Barrett's esophagus and in cases with malignant degeneration will vary depending upon the number of biopsies. Intestinal metaplasia is present in all of our cases which develop malignancy. These findings strongly suggest that the specialized type of intestinal metaplasia is the type most likely to undergo malignant degeneration. However, we observed dysplasia in all types of epithelium (IT, CT, FT). Others do not always report intestinal metaplasia in cases of adenocarcinoma arising in Barrett's esophagus.³⁰ No dysplasia adjacent to the carcinoma is noted in 4 of our 20 patients, possibly the result of destruction of dysplastic epithelium by the carcinoma.

Of special interest is the finding in two patients that squamous epithelium regenerates in zones of previous Barrett's epithelium. In the previous report by Brand, et al., the technique of demonstrating regeneration of squamous epithelium can be criticized because the biopsies are obtained with suction capsules without knowledge of the precise location of the biopsy and its relationship to the squamo-columnar junction. The finding in two of our cases that the squamo-columnar junction can be reset distally, shortly following antireflux repair, suggests that this can be a mechanical sequel to the surgery and need not represent true regeneration of mucosa. However, the visual and biopsy findings in our two patients are convincing and suggest a mechanism for squamous cell regeneration actually replacing areas of columnar epithelium by superficial overgrowth, with submergence and diminution in the glandular epithelium.

Whether the glandular epithelium will persist deep to the squamous layers, gradually atrophy and disappear completely, or even persist and become malignant is unknown.

Based upon the findings in this study and available published information, all patients identified to have Barrett's esophagus by the strict definition given should undergo quantitative testing for gastroesophageal reflux. If abnormal reflux, intestinal type metaplasia, and any degree of progression towards dysplasia is observed, an antireflux repair should be performed regardless of symptoms. Patients must remain under long-term follow-up and have correction of the reflux demonstrated, as well as rebiopsy of the mucosa and/or cytological studies at intervals. Patients with symptomatic reflux demonstrating zones of ulcerative esophagitis, ulceration in Barrett's mucosa, or stricture should be treated surgically to correct the reflux. In most instances, the stricture is dilatable prior to operation and an antireflux repair can be expected to be successful. Patients with high grade dysplasia, which includes carcinoma *in situ*, should be considered at high risk of having carcinoma somewhere in the Barrett's epithelium.

It should be stressed that carcinoma *in situ* is the end point of noninvasive intraepithelial neoplasia, and that all grades of dysplasia, as defined here, have the potential to give rise directly to invasive carcinoma. Further, many do so without going through the morphological stage of carcinoma *in situ*. Both patients in this study with high grade dysplasia that were resected had invasive carcinoma, one of which invaded through the esophageal wall and had numerous lymph node metastases, the other which had only invasion into the submucosa and has been previously reported.³¹ Such patients should be strongly advised to undergo esophagectomy and reconstruction rather than run the risk of developing clinically invasive carcinoma which carries a grave prognosis.

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DISCUSSION

E. R. WOODWARD, M.D.: This is most certainly a timely presentation. Our profession generally is not adequately aware of the malignant potential in Barrett's mucosa. Would the authors recommend that all patients with symptomatic gastroesophageal reflux have a thorough endoscopy as a part of their initial work-up and before instituting therapy? I fear that many such patients receive, at the most, an upper G.I. x-ray examination before treatment is started. In addition, would the authors consider that the presence of Barrett's mucosa is in itself sufficient indication for antireflux? Would this be a reasonable move for cancer prevention?

In a recent paper, the authors have pointed out a strong correlation between the severity of gastroesophageal reflux and the extent of Barrett's mucosa. This certainly supports the theory that the columnar epithelium represents a metaplastic change. One would expect, therefore, that surgical correction of reflux would be followed by reversion to squamous mucosa. We have four patients followed 5 to 15 years wherein most of the thoracic esophagus is columnar-lined. Transabdominal Nissen fundoplication provided symptomatic relief and healing of the ulcers and strictures at the squamo-columnar junction. However, annual endoscopy has shown no gross change in the Barrett's mucosa. Do you suppose there are occasional congenital cases?

DR. LAWRENCE DENBESTEN (Los Angeles, California): Dave, in adenocarcinoma where do you stop the resection? Frequently the Barrett's will extend very much proximally, with significant dysplasia, and I am always troubled as to how far one chases it.

Possibly, this is another of these diseases where multi-institutional surveillance might be in order. At UCLA, we have a study wherein all patients are being evaluated in a method similar to that described, and followed linearly for an indefinite period. We certainly invite other institutions and groups to participate and pool data with us, to get some

handle on the effect on regression from antireflux procedures, and also the effect on dysplasia, or the potential for carcinoma, when successful antireflux procedures have been carried out.

DR. JOHN S. SPRATT (Louisville, Kentucky): In that there is a tendency for patients who are on potassium-losing diuretics to have earlier development of cancer from villous adenomas of the rectum, at a smaller size, I would wonder whether any of these esophagus cases were on any potassium-losing diuretics.

DR. DAVID B. SKINNER (Closing discussion): In response to Dr. DenBesten, we believe that all of the Barrett's epithelium should be resected in the malignant cases. We treat this very much the same as we do carcinoma of the esophagus, aim for 10 cm proximal and distal margins when possible, and do an extensive mediastinal resection in the favorable cases.

Dr. Spratt, we have not made the correlation with potassium-losing diuretics. I am not aware that any of our patients have been treated with that, but we will certainly go home and double-check that observation.

Dr. Woodward asked about endoscopy in the initial work-up of a patient with symptomatic gastroesophageal reflux. We believe patients with reflux should be endoscoped before a decision is made about treatment, since the degree of ulcerative esophagitis cannot be predicted by the type of symptoms, and patients with ulcerative esophagitis must be followed much more closely and tightly, and probably should undergo antireflux repair early in the course of their disease. Early endoscopy will then clearly detect Barrett's if you are looking for it, although some of our patients have been endoscoped several times by other endoscopists before we saw them, and the Barrett's was not always identified. So it has to be looked for to be seen.

Dr. Woodward also commented about our policy for antireflux surgery

in Barrett's. In these patients, if they do have severe reflux documented by pH testing, or the complications of reflux, we definitely advocate antireflux surgery, followed by careful, long-term follow-up to be sure that the reflux is actually controlled. This cannot reliably be done by symptomatic analysis alone, as our two asymptomatic refluxing cases show. In spite of being asymptomatic, they had persistent reflux, and have had a progression in their dysplasia. We would not have known that if they had not been brought back for follow-up testing and biopsy.

Now, Dr. Woodward talked about the patient with the high columnar esophagus treated by Nissen fundoplication, without reversal of the line of demarcation. The international point of view on this, in Europe, this country, and elsewhere, is that the Barrett's is irreversible. However, these findings that we have seen now in two cases lead us to question whether the reversibility can be spotted unless multiple biopsies are taken. Also, the two cases reported here still have a persistent squamocolumnar junction at the same level where it originally was, but squamous epithelium was growing in thin sheets which were barely visible to the endoscopist in the lower esophagus, in areas that had clearly been lined with Barrett's epithelium previously. So if you do not do multiple biopsies, you may miss this phenomenon of squamous regeneration that we are now reporting. This is different from resetting the squamocolumnar junction distally.

There is one other report in *The New England Journal* by Brand and

associates which claims to show reversion of Barrett's epithelium to squamous epithelium. However, that study was done with blind suction capsule biopsies taken by measurement from the incisors to a level in the esophagus that had previously contained Barrett's.

We have two other patients in whom repair of a large hiatal hernia as part of the antireflux operation clearly lowered the squamocolumnar junction by elongating the esophagus. That was confirmed by early postoperative endoscopy, and the squamocolumnar junction in those two patients has not changed subsequently. It may be a little misleading to do blind suction biopsies to try and determine where the junction is. You really have to see what the effect of the operation is first, and then, in follow-up, determine if the squamous epithelium comes back to cover over the columnar epithelium, as we are reporting today.

Now, finally, there are a few cases in which carcinoma has been described after an antireflux repair had been done. The fact that our patients who are asymptomatic but show progression of dysplasia and have persistent asymptomatic reflux points to a pitfall there. The fact that the patient is asymptomatic after an antireflux repair does not mean that they are protected against continuing reflux and the possibility of the malignant process continuing. These patients must undergo pH testing as part of their routine follow-up study, to show that the operation was, in fact, successful in controlling reflux objectively, as well as relieving symptoms and complications.

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